Therapeutic Options for Mild to Moderate COVID-19 Patients

Questions and answers for health care providers

1. Where can I find an overview of the clinical guidance about new therapeutics for COVID-19?

The BC COVID Therapeutics Committee reviews the evidence and has created detailed guidance documents. For a comprehensive overview, please see the full guide developed by the BC COVID Therapeutics Committee: Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19

2. Who are the treatments currently recommended for?

In alignment with recommendations from Public Health Agency of Canada (PHAC) and the Canadian Agency for Drugs and Technologies in Health (CADTH), these treatments are currently recommended for people who have an increased risk of hospitalization for COVID-19. The CTC has worked with BCCDC to obtain data on the absolute risk for hospitalization from Omicron (excluding those who are incidentally diagnosed) in patients in BC, and how age, vaccine status and co-morbidities impact this risk. Treatment is recommended in patients who have a 5% chance or greater of being hospitalized from COVID-19. Additionally, treatment is suggested in those who have a slightly increased hospitalization risk (3-4%). Taken together, the expanded eligibility criteria are:

- Individuals who are immunocompromised or have high-risk conditions identified as Clinically Extremely Vulnerable (CEV) regardless of vaccine status or previous infection
    - *Not all children ages 12-17 who are CEV will benefit from treatment. Paxlovid is not recommended below the age of 18 at this time. Those with multiple co-morbidities would have the highest potential benefit and are eligible only for sotrovimab*
- Unvaccinated individuals without previous infection who are EITHER:
    - ≥50 years OR
    - have three or more chronic conditions/co-morbidities
- Individuals ≥ 50 years with 1-2 vaccine doses or previous infection alone, with three or more chronic conditions/co-morbidities
- Individuals aged ≥70 years with 1-2 vaccine doses or previous infection alone, with one or more chronic condition/co-morbidity
- Individuals ≥ 70 years with three or more chronic conditions/co-morbidities regardless of vaccine status or previous infection
- Indigenous individuals (if not captured above) who are EITHER:
    - unvaccinated without previous infection OR
    - ≥ 50 years with 1-2 vaccine doses or with previous infection alone OR
    - ≥ 70 years regardless of vaccine status or previous infection

To determine an individual's risk for hospitalization, see Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19. A point system or a thermal map that characterizes the risk based on different factors has been developed.

Pregnancy and Breastfeeding: Currently available therapies have not been evaluated in pregnancy or breastfeeding. Prescribers may consult Reproductive Infectious Disease on call at BC Women's Hospital if prescribing COVID-19 therapy, especially nirmatrelvir/ritonavir.

Patients are encouraged to use protection while taking these medications. In addition, those on oral contraceptives should use a back-up method when taking nirmatrelvir/ritonavir due to drug interactions leading to lower plasma levels of estrogen.

Pediatrics: nirmatrelvir/ritonavir (Paxlovid) is not currently approved for children under 18 years. All cases in which remdesivir or sotrovimab is being considered should be discussed with, and approved by the Pediatric Infectious Diseases physician on call at BC Children's Hospital.

3. What are the symptom windows in which these antiviral therapies are most beneficial?

Symptom windows vary with each therapeutic agent and follow study inclusion criteria:

- Nirmatrelvir/ritonavir (Paxlovid) should be given within 5 days of symptom onset
- Remdesivir should be given within 7 days of symptom onset
  Sotrovimab (Xevudy) should be given within 7 days of symptom onset

**It is appropriate to allow the addition of adequate time for delivery of medication for those living in remote and rural communities*
***It is appropriate to extend the treatment window to 7 days for nirmatrelvir/ritonavir if the patient's symptoms exceed 5 days and they would otherwise be referred for remdesivir solely based on its longer treatment window.*

4. What are some of the contraindications?

- **Nirmatrelvir/ritonavir (Paxlovid)** should not be used in end-stage liver disease (Child-Pugh C), severe renal disease (eGFR < 30ml/min). In patients with hepatitis B and C, or HIV infection regardless of treatment status, Specialist Consultation (e.g., Infectious Diseases, HIV Specialist) is recommended, but should not delay treatment.
  - **Many drug-drug interactions contraindicate the use of nirmatrelvir-ritonavir**, most common include amiodarone, DOACs, statins, some antipsychotics, midazolam and triazolam, as well as illicit drugs; especially fentanyl and methamphetamine. Patients with hypersensitivity to ritonavir or other protease inhibitors should not be prescribed nirmatrelvir/ritonavir.
    Drug interactions must be verified and a management plan in place before prescribing-
    *see Practice Tool #3: Drug Interactions and Contraindications

- **Remdesivir** (Veklury) is not known to cause hypersensitivity or infusion reactions, but they are theoretically possible. Remdesivir is co-formulated with cyclodextrin, an additive that can accumulate in renal disease and is not officially approved for those with eGFR < 30 ml/min. However, experts agree that a 3-day course is safe to use in end-stage renal disease and dialysis. Remdesivir is also contraindicated if the ALT is 5 X ULN.

- **Sotrovimab** (Xevudy) is known to cause hypersensitivity reactions and infusion reactions, although they are rare. Sotrovimab is contraindicated in those who are hypersensitive to this drug or to any ingredient in the formulation: if reactions develop during the 1-hour infusion, the infusion should be stopped.

5. Who can I call for help?

Call **COVID Antivirals Support Line for Clinicians and Pharmacists** if you have questions about drug interactions

A provincial pharmacy line has been established to support the arrival of the new COVID-19 medications in BC, nirmatrelvir/ritonavir (Paxlovid), remdesivirand sotrovimab. There are a few requirements that doctors need to know when it comes to prescribing, including the treatment window, how they contradict or interact with other medications, etc. In addition, a prescriber and/or a pharmacist must assess each prescription against drug interactions and medical contraindications. This provincial pharmacy line will support prescribing and pharmacists to dispense these novel medications.

For expert pharmacist advice, please call 1-866-604-5924 (Monday – Friday, 8:30am – 4:30pm). A clerk will answer your call (or leave a voicemail) and arrange a pharmacist to call you back. Calls will be responded to as soon as possible during office hours.

Be ready to provide:

- Clinician/pharmacist details: Name, phone number, city where you practice, and when is a good time to call you back.
- Patient details: Name, date of birth (DoB), personal health number (PHN), and any relevant medical info

6. Is there updated research on the effectiveness of Remdesivir (Veklury) for mild to moderate illness?

The following summarizes some key points from the BC CTC's clinical guidance, and the landmark trial (PINETREE) of remdesivir (Veklury) which was published in the December of 2021 in the New England Journal of Medicine. It's important to say that these studies were completed prior to Omicron, and therefore we will be watching to learn more about the efficacy of this new therapy as it become available:

- This medication is a direct-acting anti-viral made up of two agents. Its active form acts like a nucleoside used to build RNA and inhibits the RNA-dependant RNA polymerase, stopping viral replication
- Remdesivir is an intravenous antiviral initially evaluated in severely ill inpatients with COVID-19 requiring oxygen support, and later evaluated for mild-moderate COVID-19 with a shorter, 3-day duration of treatment
- The PINETREE trial evaluated remdesivir in 562 mildly-moderately ill outpatients
- Patients were randomized to receive remdesivir 200mg IV on day 1, followed by 100mg on days 2 and 3 or placebo and evaluated in a double-blind fashion
- Patients were included if they presented within the previous 7 days and who had at least one risk factor for disease progression (age >60 years, obesity, or certain coexisting medical conditions)
- The trial was stopped when only 45% of the planned population was recruited due to widespread use of vaccination and the availability of proven treatments making randomization to placebo ethically challenging
- The primary outcome was COVID-19-related hospitalization or death from any cause
- 2 of 279 patients (0.7%) in the remdesivir group and in 15/283 (5.3%) in the placebo group met the primary endpoint, p=0.008.
- This equated to an 87% relative risk reduction, a 4.6% ARR and a NNT of 22, which is slightly higher than nirmatrelvir/ritonavir or sotrovimab (17 and 20, respectively).
- A total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a COVID-19-related medically attended visit by day 28 an no patients died by day 28.
- Remdesivir was generally well tolerated; transaminases may need to be monitored if those with baseline liver enzyme elevations. Remdesivir has been widely given to patients with renal disease with and without dose adjustments, although such patients have been excluded from RCTs and are not reflected in the Canadian labeling

Remdesivir has the advantage of having few drug interactions while maintain comparable risk reductions to nirmatrelvir/ritonavir. However, the 3-day IV dosing regimen challenging to administer, and as such, it is recommended only to the highest-risk patients (those with a hospitalization risk of ≥ 5%) if nirmatrelvir/ritonavir cannot be given due to contraindications or drug-drug interactions. To determine an individual's risk for hospitalization, see Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19. A point system or a thermal map that characterizes the risk based on different factors has been developed.

7. Is there updated research on the effectiveness of Nirmatrelvir/Ritonavir (Paxlovid) for mild to moderate illness?

The following summarizes some key points from the BC CTC's clinical guidance, and the landmark trial (EPIC-HR) of nirmatrelvir/ritonavir (Paxlovid) which was published in February 2022 in the New England Journal of Medicine. It's important to say that these studies were completed prior to Omicron, and therefore we will be watching to learn more about the efficacy of this new therapy as it become available:

- This medication is a direct-acting anti-viral made up of two agents. It belongs to the protease inhibitor (PI) class and is similar to PIs used to treat HIV
- Nirmatrelvir/ritonavir was studied in a double-blind placebo-controlled trial, "EPIC-HR" of 2246 unvaccinated outpatients with mild to moderate COVID-19 within 5 days or less of symptom onset.
- Participants deemed at risk of disease progression to requiring hospitalization were enrolled. This included unvaccinated individuals who were either 55 years or older or who had a chronic condition such as hypertension, diabetes, lung disease or obesity. The median age of participants in the trial was 46 and the most common risk factor present was smoking, followed by hypertension. Patients were excluded if they had any potential drug-drug interactions.
- The primary endpoint was COVID-19 related hospitalization (not all cause) or death from any cause.
- Results: 0.8% (approximately 1%) (8/1039) patients in the treatment group vs 6.3 % (66/1064) in the placebo arm experienced the primary endpoint (nearly all events were hospitalizations and not death). Therefore, the absolute risk reduction is 5.5% (with a relative risk reduction of 88%) and a Number-Needed-to-Treat of 18.
- The rate of hospitalization from any cause and the rate of mortality has not yet been reported.
- Drug has been shown to cause nausea, diarrhea and taste disturbances more frequently than placebo, with an adverse effect rate attributed to drug vs. placebo of 7.8% vs. 3.8% respectively

8. What are some of the challenges in prescribing Paxlovid?

Patients who are COVID-19 positive and in the first 5 days of their symptoms can be considered for Paxlovid.

One of the challenges is that for those who potentially have the greatest benefit from Paxlovid, there are also risks with respect to prescribing related to their underlying disease and drug-drug interactions with their medication.

While there is evidence of benefits, Paxlovid has many drug-drug interactions, some of which are serious. This includes drugs such as immunosuppressants used in transplant, some cancer drugs and more common drugs such as anti-coagulants, statins and others. There are also serious consequences with the use of opioids that must be considered. Additionally, the patient's renal function must be considered and the medical risks and benefits of potentially holding or reducing the dose of some of their usual medications to facilitate the use of Paxlovid. This means that prescribing this medication requires careful review of the patient, their symptoms, the risk of COVID-19 and the risk of interactions or alterations to their current medications and discussion of those risks with the patient. See the Practice Tool #3 – Drug-drug Interactions to learn more about these considerations.

9. Is there updated research on the effectiveness of Sotrovimab (Xevudy) for mild to moderate illness?

The following summarizes some key points from the BC CTC's clinical guidance document. It is expected that evidence will continue to develop and therefore be sure to watch for changes to this evidence. It's important to say that these studies were completed prior to Omicron, and therefore we will be watching to learn more about the efficacy of this new therapy as it becomes available:

- Sotrovimab is a monoclonal antibody with retained activity against Omicron. It's ability to neutralize the BA.2 variant, has become prevalent in BC, is reduced by 16-48-fold. On March 25, 2022, the Food and Drug Administration (FDA) revoked the authorization for sotrovimab in regions where BA.2 prevalence exceeds 50%. This was done based on an abundance of caution, taking the highest reduction in binding (48-fold) and the lowest possible lung penetration (10%). The CTC concluded that sotrovimab likely still retains some efficacy under most circumstances; however, the totality of data is stronger for other agents.
- There has been a single peer-reviewed double blind randomized placebo-controlled manufacturer sponsored trail (COMET-ICE). Prior to Omicron, 1057 unvaccinated outpatients with mild-moderate symptoms and at least one risk factor of disease progression (e.g. age >60, obesity, hypertension, diabetes) were randomized.
- They received a 500mg IV infusion compared to placebo within 3-7 days of symptom onset.
- The primary endpoint was a composite outcome of all-cause hospitalization for >24 hours or death within 29 days of receipt of infusion.
- Results: 6/528 patients met the primary outcome in the treatment group compared to 30/529 in the placebo group (1% vs 6%), with an absolute risk reduction of 5% and Number-Needed-To-Treat of 20. There were two deaths, both in the placebo arm.
- Secondary outcome showed reduced progression to severe respiratory disease of 1% vs 5% on the basis of symptoms.
- Sotrovimab did not reduce the length of stay or ICU- bed days.
- 6 patients in each group had infusion reactions.
- While all the study participants were >18 years, the manufacturer has submitted sufficient pharmacokinetic and pharmacodynamic data to Health Canada to authorize inclusion of patients 12-17y weighing at least 40kg.
- Health Canada is currently evaluating a 1000mg dose that has been proposed to overcome the reduction in binding. Guidance regarding sotrovimab's ongoing role in therapy and dosing considerations are forthcoming.
- Currently the CTC recommends that if sotrovimab is **used in extenuating circumstances** as a last line agent where potential of benefit outweighs the risk, disclosure to patients of risks and benefits in consideration of individual circumstances (clinical status, patient values, logistics) is necessary. Sotrovimab should not be chosen solely for convenience reasons.

10. What type of testing is required?

A positive test result is required. Polymerase Chain Reaction (PCR) is the preferred diagnostic test, especially in the first 1-2 days of symptoms when a RAT is more likely to be falsely negative. However, a positive Rapid Antigen Test (RAT) is acceptable.

11. Do patients need to be symptomatic?

Yes. Patients offered treatment should be appreciably symptomatic from COVID 19. Treatment is unlikely to benefit those who are mildly ill and improving on their own. Therapies should not be prescribed to asymptomatic patients.

A great deal of case-by-case clinical judgement is required to discern whether mild symptoms warrant treatment.

Patients who are moderately ill, i.e., showing evidence of lower respiratory disease during clinical assessment such as shortness of breath or imaging suggestive of pneumonia, are the most likely to progress to severe illness.

12. Are there any materials to help me counsel my patients on antiviral therapies?

Patient information sheets for nirmatrelvir/ritonavir (Paxlovid), remdesivir (Veklury) and sotrovimab (Xevudy) are available on the BCCDC website: http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/patient-handouts

- Patient Information about (nirmatrelvir/ritonavir) Paxlovid
- Patient Information about remdesivir (Veklury)
- Patient Information about sotrovimab (Xevudy)

In addition, there is a self-screening tool posted publicly that allows patients to find out if they might benefit from COVID-19 antiviral therapies.

Materials for providers:

- Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19
- Provider Summary
- Practice Tool 1 – Assessment Steps
- Practice Tool 2 – CEV Definitions
- Practice Tool 3- Drug Interactions and Contraindications
- Standardized Paxlovid Rx

13. What do I need to know about monitoring and evaluation?

Patients should call you back if they have any concerns. With the newness of this drug, BC has taken the proactive approach of contacting all patients who receive Paxlovid over the next three months to follow-up with each patient: identifying whether there were adverse drug events, compliance with the 5-day treatment course, and patient outcomes. This evaluation will provide us with useful information as we learn more about Paxlovid and future COVID therapies.