

COVID-19 therapies for mild to moderately ill patients

Recently, two novel agents have become available in BC for the treatment of COVID-19 in mild to moderately ill patients: a direct-acting oral antiviral, nirmatrelvir/ritonavir, and an IV antiviral, remdesivir. A monoclonal antibody, sotrovimab, was also in widespread use until recently; however, its utility has been limited due to loss of activity against the BA.2 variant of Omicron. On 23 March 2022, due to increased drug supply and operational capacity, eligibility criteria were expanded to include all symptomatic COVID-19 individuals in BC who are at increased risk of severe illness and hospitalization. Nirmatrelvir/ritonavir and remdesivir were each evaluated in a randomized controlled trial conducted during the Delta wave in unvaccinated adults with a risk factor for severe COVID-19, such as being over 55 years of age or having a comorbidity.^{1,2} Adults were offered treatment if they had mild to moderate COVID-19 and were within 5 (nirmatrelvir/ritonavir) or 7 days (remdesivir) of symptom onset. Both treatments demonstrated a significant reduction in progression to hospitalization over placebo (6.3% versus 0.8% for nirmatrelvir/ritonavir and 5.3% versus 0.7% for remdesivir).^{1,2} As Omicron causes less-severe disease than Delta and nearly 90% of BC adults have received a COVID-19 vaccine, patients who would derive a clinically meaningful benefit need to be carefully selected rather than applying trial inclusion criteria when choosing to offer treatment.

Who is at risk for hospitalization from COVID-19 in BC during the Omicron wave?

In BC, the average risk of hospitalization in the Omicron wave decreased to 1.2% from the 6.3% observed during the Delta wave in patients who were tested by polymerase chain reaction (PCR).³ In addition, an analysis conducted by the BCCDC of hospitalized patients from 3 January 2022 to 9 February 2022 demonstrated that approximately 60% of hospitalizations after testing positive were incidentally diagnosed rather than being caused by severe COVID-19.⁴ The COVID-19 Therapeutics Committee has developed a set of BC-specific eligibility criteria to identify individuals who would be expected to benefit from these treatments based on local epidemiological data.^{3,4}

Who is eligible to receive COVID-19 treatments?

Adjusting for hospitalization rates, vaccination status, and symptomatic versus incidental COVID-19 diagnosis, individuals who are at increased risk include those who are severely immunocompromised or have a combination of risk factors such as advanced age, lack of or incomplete immunization, and chronic conditions/comorbidities. Individuals who demonstrated at least a 3% risk of hospitalization in this analysis are currently eligible to receive treatment. Patients eligible for therapy have also been prioritized for PCR testing; however, a positive rapid antigen test is acceptable for diagnostic purposes [Table].

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TABLE. Eligibility for COVID-19 treatment by age, vaccine status, and number and type of risk factors.

Age	Number of vaccine doses and/or previous infection		
	0, and no previous infection	1 to 2, or previous infection alone	3, or previous infection and any vaccination
Any adult ≥ 18	Those clinically extremely vulnerable defined as CEV 1, CEV 2, and CEV 3		
18–49	If ≥ 3 risk factors or Indigenous	Not at increased risk	Not at increased risk
50–69	At increased risk	If ≥ 3 risk factors or Indigenous	Not at increased risk
70+	At increased risk	If ≥ 1 risk factor or Indigenous	If ≥ 3 risk factors or Indigenous

Legend

At increased risk: Treatment is recommended/suggested

Not at increased risk: Treatment is not recommended

CEV 1: e.g., solid organ transplant, bone marrow or stem cell transplant, treatment for hematological malignancy, anti-CD20 or B-cell-depleting therapies

CEV 2: e.g., receiving immunosuppressive agents, moderate–severe primary immunodeficiency, cancer treatment for solid tumors, advanced HIV

CEV 3: e.g., cystic fibrosis, severe asthma or COPD, diabetes requiring insulin, intellectual and developmental disabilities, rare blood disorders, dialysis

Indigenous individuals may be at risk for disease progression due to disparate rates of comorbidity, including undiagnosed risk factors, and social determinants of health.

Source: Framework for COVID-19 Therapeutics for Mild-Moderately Ill Patients, BC COVID-19 Therapeutics Committee.

This article is the opinion of the BC Centre for Disease Control and the BC COVID-19 Therapeutics Committee and has not been peer reviewed by the BCMJ Editorial Board.

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What are practical considerations with offering treatment?

Any prescriber in BC can now prescribe nirmatrelvir/ritonavir. Patients need to be within 5 days of symptom onset to qualify, which can be extended to 7 days for those who would otherwise be referred for IV treatment solely on the basis of the treatment window. Those who are unable to see their family physician in time can be referred to the centralized COVID-19 Assessment and Treatment e-team (CATE) at 1 888 COVID-19.

Ritonavir and, to a lesser extent, nirmatrelvir are potent CYP3A4 inhibitors and interact with many medications that are metabolized through this pathway or are enzyme inducers. Common drug-drug interactions that either contraindicate the use of nirmatrelvir/ritonavir or require modification include those with amiodarone, anticoagulants rivaroxaban and apixaban, immunosuppressants tacrolimus and cyclosporine, statins, certain antipsychotics and antiepileptics, calcium channel blockers, and

fentanyl.⁵ A medication review is necessary for most patients, and a pharmacy consultation is recommended if significant interactions are present. A recent Canadian study demonstrated that 68% of older adults eligible for treatment with nirmatrelvir/ritonavir had a drug-drug interaction and 21% were taking at least one inappropriate medication.⁶ Since patients who are at risk of hospitalization from COVID-19 are elderly with chronic conditions on multiple therapies, probability of drug-drug interactions with nirmatrelvir/ritonavir is high, highlighting the importance of a comprehensive assessment of drug-drug interaction and proactive deprescribing prior to prescribing nirmatrelvir/ritonavir to ensure patient safety.

Remdesivir is the only available alternative for those with significant drug-drug interactions, and unlike sotrovimab, which is variant specific and prone to resistance with emerging variants of concern, remdesivir is a nucleoside analogue, which is stable against SARS-CoV-2 mutations. Additionally, the intravenous administration requires a referral to a health care facility at a local health authority for three daily 30-minute infusions. During the assessment of the first 200 patients who contacted Service BC for nirmatrelvir/ritonavir, approximately 30% of patients who were eligible for therapy were referred for an alternative IV treatment due to drug-drug interactions.⁷

What resources are available to clinicians?

Clinicians can access a wide range of resources to assist with patient assessment and prescribing of COVID-19 therapies. Evidence changes rapidly and resources are updated accordingly.

Nirmatrelvir/ritonavir is prescribed using a specific prescription form, available at www2.gov.bc.ca/assets/gov/health/forms/2368f1.pdf. Pharmacies that stock nirmatrelvir/ritonavir kits are listed at www.bcparmacy.ca/paxlovid.

The COVID-19 Therapeutics Committee maintains the following resources on the BCCDC website (www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/treatments):

- COVID-19 Clinical Practice Guide. A comprehensive guide that includes recommendations and supporting evidence, including local epidemiological data.

- Practice Tool #1: Step-by-Step Assessment. Practical guidance on patient selection, testing, clinical assessment, therapy management, and contact information for referrals and consultations.
- Practice Tool #2: Definitions of Clinically Extremely Vulnerable. Information for immunocompromised and other at-risk groups.
- Practice Tool #3: Drug-Drug Interactions. A color-coded table of common interactions and management tips.
- Practice Tool #4: Pharmacist Counseling Checklist. A quick-reference guide for pharmacists.

Prescribers can also access a summary of the guidance in a two-page format, as well as a provider Q&A document, both available on the BCCDC website.

The COVID-19 Antiviral Support Line for Clinicians is also available Monday to Friday, 8:30 a.m. to 4:30 p.m., at 1 866 604-5924.

Prescribers can also request a personalized education session on nirmatrelvir/ritonavir provided by the Provincial Academic Detailing service. For more information, visit www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pad-service/intro-paxlovid-nirmatrelvir-ritonavir. ■

—BC COVID-19 Therapeutics Committee

—David Patrick, MD


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