

BC COVID THERAPEUTICS COMMITTEE (CTC)

Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19

April 2025 Update: More precise definitions of high-risk patients who benefit from treatment, update on the Provincial Rapid Antigen Program, consolidation of practical information from the Step-by-Step Assessment (now archived) into one document.

GENERAL INFORMATION

About this Guide

This practice guide provides **recommendations** for use of antivirals (**nirmatrelvir/ritonavir** and **remdesivir**) for mild to moderate COVID-19. The guidance can be applied in patients across health care settings, including in outpatients, residents of long-term care and those hospitalized for non-COVID reasons who are incidentally diagnosed with mild-moderate disease. This document also touches on other therapeutics not currently in use, provides general guidance on testing, risk assessment and supporting evidence, with practical BC-specific tips for prescribers.

RECOMMENDATIONS

Who is Recommended to Receive Antiviral Treatment for Mild-Moderate COVID-19?

Patients who **test positive for SARS-CoV-2**, with **appreciable symptoms** and a non-reassuring presentation and trajectory, who are at an **increased risk for hospitalization** or progression to severe COVID-19, such as:

- Individuals with **moderate* to severe immunosuppression**, due to:
 - Solid organ transplant
 - Active treatment for a hematological malignancy
 - Allogeneic bone marrow or stem cell transplant in the last year
 - Autologous bone marrow or stem cell transplant in the last 6 months
 - Receipt of chimeric antigen receptor (CAR) T-cell therapy in the last 6 months
 - Receipt of anti-CD-20 or B-cell depleting agents in the last 2 years¹
 - Receipt of moderately immunosuppressive agents²
 - Receipt of systemic treatment for cancer, including for solid tumors, in the last 6 months (3 months for hormonal therapy)
 - Moderate-severe primary immunodeficiency
 - Advanced or untreated HIV
- Individuals **≥60 years** who have **serious medical conditions**, who have been shown to significantly and consistently benefit from antivirals, such as those with:
 - End-stage renal disease (eGFR < 30ml/min or dialysis)
 - Diabetes treated with insulin

- Severe or end-stage lung conditions such as COPD, asthma, interstitial lung disease, cystic fibrosis, or neurological conditions requiring Bi-Pap or ventilation
- Severe intellectual or developmental disabilities
- Rare blood and genetic disorders such as sickle cell disease, thalassemia, urea cycle defects

* Individuals **younger than 60 years** with a moderately immunosuppressive condition such as prostate or breast cancer or an immunological condition treated with a single moderately immunosuppressive drug² have not been shown to routinely benefit from treatment with antivirals. Clinical judgement and consideration of other risk factors is strongly recommended.

1. **Severely immunosuppressive agents: Anti-CD-20 agents:** rituximab, ocrelizumab, ofatumumab, obinutuzumab, ibritumomab, tositumomab; **B-cell depleting agents:** epratuzumab, MEDI-551, belimumab, BR3-Fc, AMG-623, Ataccept, antiBR3, alemtuzumab
2. **Moderately immunosuppressive agents: Biologics:** abatacept, adalimumab, anakinra, benralizumab, brodalumab, canakinumab, certolizumab, dupilumab, etanercept, golimumab, guselkumab, infliximab, interferon products (alpha, beta, and pegylated forms), ixekizumab, mepolizumab, natalizumab, omalizumab, reslizumab, risankizumab, sarilumab, secukinumab, tildrakizumab, tocilizumab, ustekinumab, or vedolizumab; **Oral immune-suppressing drugs:** azathioprine, baricitinib, cyclophosphamide, cyclosporine, leflunomide, dimethyl fumerate, everolimus, fingolimod, mycophenolate, siponimod, sirolimus, tacrolimus, tofacitinib, upadacitinib, methotrexate, or teriflunomide; **Oral steroids on an ongoing basis:** dexamethasone, hydrocortisone, methylprednisolone, or prednisone at a dose of 20 mg/day of prednisone equivalent; **Immune-suppressing infusions/injections:** cladribine, cyclophosphamide, glatiramer, methotrexate

Therapy Recommendations

Nirmatrelvir/ritonavir is recommended within 5 days[^] of symptom onset for patients with appreciable symptoms and a non-reassuring presentation and trajectory who are at an increased risk for hospitalization or progression to severe COVID-19 due to conditions or medication above.

Recommended dosing guidance for nirmatrelvir/ritonavir based on renal function:

Last available eGFR (ml/min)	Dosing schedule
60 or above	Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days
30 to 59	Nirmatrelvir/ritonavir 150/100mg PO BID x 5 days
Less than 30 (no dialysis)	Nirmatrelvir/ritonavir 300/100mg PO once daily on day 1, then 150/100mg PO once daily on days 2-5 (Pharmacist will dispense regular nirmatrelvir/ritonavir kits and remove all PM doses of 300/100mg as well as one tablet of nirmatrelvir 150mg from the AM dose on days 2-5)
Dialysis	Nirmatrelvir/ritonavir 300/100mg PO once daily on day 1, then 150/100mg PO once daily on days 2-5, given after dialysis on dialysis days (Pharmacist will dispense regular nirmatrelvir/ritonavir kits and remove all PM doses of 300/100mg as well as one tablet of nirmatrelvir 150mg from the AM dose on days 2-5)

NOTES:

[^]The symptom window for nirmatrelvir/ritonavir can be extended to 7 days in outpatients if they would otherwise be referred for remdesivir solely based on its longer treatment window.

Remdesivir is recommended within 7 days of symptom onset as an alternative to nirmatrelvir/ritonavir if nirmatrelvir/ritonavir cannot be given due to drug-drug interactions or contraindications ([See Practice Tool – Drug Interactions and Contraindications](#)).

Recommended dosing guidance for remdesivir based on renal function:

Most recent eGFR (ml/min)	Dosing schedule
30 or above	Remdesivir 200mg IV once daily on day 1, followed by 100mg IV once daily on days 2 and 3
Less than 30 (no dialysis)	Remdesivir 200mg IV once daily on day 1, followed by 100mg IV once , 48 hours later
Dialysis	Remdesivir 200mg IV once daily on day 1 post-dialysis, followed by 100mg IV once post dialysis, 48-72 hours later

NOTES:

The decision to offer remdesivir vs. off-label nirmatrelvir/ritonavir in those with eGFR <30ml/min or drug-drug interactions should be based on joint decision making between the patient and clinician in consideration of risk vs. benefit.

Inpatients with mild-moderate COVID-19 who are at increased risk of progression to severe disease due to conditions or medications above may be offered nirmatrelvir/ritonavir or remdesivir based on contraindication, drug-drug interactions, IV access and planned length of stay. Patients should complete the antiviral started as there are no data to guide switching between antivirals midway through the treatment course.

Patients need to be referred to the nearest Health Authority infusion clinic for remdesivir administration:

- Fraser Health Authority: Directly order infusions. Forms are accessible on the FH Medical Staff website: JPOCSC Clinics & Services Forms -> Medical Day Care -> COVID-19 Therapy Pack. Fax to JPOCSC MDC 604-582-3742. If you need consultation, connect through RACE www.raceapp.ca Infectious Disease - COVID-19 Clinical. Requests will be returned by phone.
- Vancouver Coastal and Providence Health: Please make the referrals for remdesivir infusions through the CATe line at 1-888-COVID19
- Interior Health Authority: Contact the Interior Health COVID Therapeutics Virtual Clinic at 250-258-7369 or at COVIDTherapeutics@interiorhealth.ca
- Island Health: COVID-19 therapeutics clinic: 250-737-2030 (ext 44685) OR RJH ID on call
- Northern Health: CATe physician to consult the NH Remdesivir referral document as phone numbers and processes vary by site

Expected Benefit

Patients who meet the high-risk criteria above had a risk of hospitalization of ~3% at the start of the Omicron waves, and treatment reduced this risk by about half. This means treatment has an absolute risk reduction of 1.5%, and number-needed-to-treat of 67 (NNT). This baseline risk is likely lower now, which increases the NNT and decreases the therapeutic value of antiviral treatment.

Reasons to Not Use Antivirals for COVID-19

Nirmatrelvir/ritonavir or remdesivir are not recommended in the following situations:

- Antivirals have been shown to have no impact on symptom duration and severity and **should not be used to alleviate or hasten symptom resolution.**
- Multiple studies have shown that antivirals do **not prevent the risk of developing post-COVID condition** (i.e., long COVID) or significantly reduce mortality. Antivirals should be prescribed with the goal of preventing progression to severe COVID-19.
- Recent studies continue to show that **antivirals do not improve symptoms of post-COVID condition (long COVID).**
- Randomized controlled trials have shown that antivirals **are ineffective as pre- or post-exposure prophylaxis** in case contacts. Antivirals should only be used for treatment of acute COVID-19.
- Antivirals have been evaluated in patients who are appreciably symptomatic. Antivirals **should not be used in patients who are asymptomatic, have only mild cold symptoms or who are improving on their own.**
- The duration of **antiviral treatment should not be routinely prolonged, or courses repeated.** High-risk patients who have recalcitrant infection, fail monotherapy or relapse should be managed in consultation with an appropriate expert (e.g., infectious diseases specialist, transplant infectious diseases specialist).

Practical tips on managing those in whom treatment is not recommended:

COVID has been a major source of misinformation and media attention. The biggest challenge faced by clinicians regarding COVID therapeutics is counselling patients who expect antiviral treatment but in whom treatment is not going to be beneficial. Strategies used by clinicians to support antimicrobial stewardship (e.g., not prescribing antibiotics for otitis media) can be employed to have informed conversations. The following tips can be used when discussing antiviral treatment with patients:

- Inform patients that their absolute risk of hospitalization is below a fraction of a % and that antivirals cannot reduce that any further
- Dispel misinformation such as that antivirals save lives, make people feel better faster or prevent post-COVID condition (long COVID)
- Share scientific resources such as the recent [Therapeutics Initiative letter](#) that reiterates these points
- Educate patients that the risk of a side-effect such as nausea, vomiting and taste disturbances is ~25%. In BC, about one in 10 patients does not finish Paxlovid or discontinues it due to side effects
- If drug-drug interactions with ritonavir are present, counsel patient on the risk vs. benefit
- Use the “Watchful Waiting” approach: ask those at high-risk with mild symptoms to self-monitor, reiterating that there is a 5-day treatment window and treatment may be initiated if they worsen
- Ask patients to recall what happened when they had COVID in the past. If they have recovered, reassure them that they will likely recover again and now have stronger hybrid immunity
- Discuss the importance of vaccination (both for COVID-19 and influenza) and assure patients that the “match” against currently circulating variants is excellent
- Use the opportunity to motivate patients to manage or prevent chronic conditions appropriately to further reduce their chance of severe disease

- Some patients respond to cost information and want to contribute to a cost-effective health care system. In such cases, share that Paxlovid costs \$1,500 a course and not prescribing it when there is no benefit helps fight the ballooning costs of health care
- Acknowledge the impact of direct-to-consumer advertising by the manufacturer of nirmatrelvir/ritonavir or social media, and inform patients that such advertising is intended to evoke emotions to sell a product and not provide scientific information

For patients who simply want a product, recommend a **saline nasal spray, 1-2 sprays into each nostril QID for the duration of the illness**. While the quality of evidence is moderate, various studies show that saline nasal irrigation reduces symptoms and decreases viral loads and carries little costs and no harm.

Monoclonal Antibodies (mAbs) such as **sotrovimab** are **not recommended**. Due to reduced binding to Omicron, there are currently no mAbs in Canada that have reliable activity against circulating variants of concern. The role of monoclonal antibodies is limited to combination therapy in refractory or recalcitrant COVID-19 in patients who are severely immunocompromised and remain non-immune despite vaccination. In such cases, mAbs would need to be ordered through the Special Access Program by a clinician with appropriate expertise, and the variant of concern would require genotypic identification so that the activity of the mAb can be confirmed.

Inhaled corticosteroids are **not recommended**. A recent, well-conducted randomized placebo-controlled trial (ACTIV-6) showed that inhaled fluticasone had no impact in symptom duration and severity in patients infected with the Omicron variant. No difference in hospitalization or mortality was seen, and participants receiving fluticasone had numerically more health-care related visits than those randomized to placebo. Older studies of inhaled corticosteroids (STOIC, PRINCIPLE) have significant limitations such as a lack of blinding, low generalizability or negative primary endpoints.

Tixagevimab/cilgavimab is **not recommended**; it has demonstrated a 50.5% relative risk reduction (RRR) in COVID-19 hospitalization and death in unvaccinated, non-hospitalized adults with mild- moderate COVID-19 (TACKLE), which is lower than the RRR seen with other COVID-19 treatments in similar trials.

Tixagevimab/cilgavimab is ineffective against many currently circulating variants of Omicron where 300-1000-fold reductions in binding are seen.

Molnupiravir is **not recommended** (if/once available in Canada); if used on a case-by-case basis in patients who are unable to receive nirmatrelvir/ritonavir, sotrovimab or remdesivir, the uncertainty of benefit and the absolute risk of hospitalization, including factors such as age, number and type of co-morbidities and severity of symptoms need to be considered.

Colchicine is **not recommended** due to low certainty of benefit, potential risk of adverse events, and additional immunosuppression in this population.

Fluvoxamine is **not recommended** due to low certainty of benefit and potential risk of adverse events associated with the dose evaluated (100mg PO BID), especially in vulnerable and elderly patients.

Natural health products such as antioxidants, probiotics and vitamins are not recommended due to poor quality data supporting their use and/or lack of demonstrated benefit.

EVIDENCE and PRACTICAL CONSIDERATIONS

Risk Assessment and Evidence

Early randomized trials of antivirals ([EPIC-HR](#) for nirmatrelvir/ritonavir, [PINETREE](#) for remdesivir) took place before wide-spread COVID vaccination, presence of natural immunity and emergence of the Omicron variants. Participants who had a single additional risk factor such as advanced age or a chronic condition experienced a hospitalization rate from COVID-19 of approximately 5-6% once they were diagnosed with mild-moderate disease. Antivirals were successful in reducing the risk of progression to severe disease by 80-90%, to approximately 1%.

The ability of antivirals to further reduce the risk of hospitalization or progression of COVID-19 below a single percentage point is questionable. A recently published randomized controlled trial ([EPIC-SR](#)) compared nirmatrelvir/ritonavir to placebo in patients at standard risk for disease progression. Patients were enrolled into the trial if they were either unvaccinated or were vaccinated and had a risk factor such as age over 50 years or a chronic condition. The trial began during the Delta wave of the pandemic and continued until into the first months of Omicron. Patients enrolled in the Delta waves who received nirmatrelvir/ritonavir experienced a hospitalization rate of approximately 0.7% (3/428) vs. 2.4% (10/426) if they received placebo ($p=NS$). However, upon the emergence of Omicron, only 2 additional events occurred in the trial, both in the nirmatrelvir/ritonavir arm, for a final hospitalization rate of 0.8% (5/654) vs. 1.6% (10/634) in the placebo arm ($p=NS$). The trial stopped due to futility as the event rate approached zero in the Omicron waves.

Currently, the risk of hospitalization and mortality in British Columbia after testing positive for SARS-CoV-2 is below a fraction of a percent. An [analysis](#) by the BCCDC showed that in 2023, a first ever COVID-19 infection carried an average risk of hospitalization of 0.3% and a mortality rate of 1 in 1000. This risk is expected to be even lower in the general BC population now, as lack of natural immunity from previous infection is increasingly uncommon, and most patients have received at least one dose of the Omicron-specific mRNA vaccine which continues to confer strong protection against the currently circulating variants.

Some patients, however, continue to experience significant burden of disease where early treatment with antivirals is warranted and shown to be effective. For example, a [2023 BC analysis](#) showed that those who were severely and moderately immunocompromised benefited from the receipt of nirmatrelvir/ritonavir with absolute risk reductions of 2.5% and 1.7% respectively. Those with high-risk conditions such as end-stage lung disease or diabetes treated with insulin also benefited from treatment, but nearly all of the events occurred in those 60 years and older. Other individuals, including elderly with less severe comorbidities, did not experience a reduction in hospitalization or mortality with early treatment with nirmatrelvir/ritonavir.

The most comprehensive [summary of evidence](#) of early antiviral treatment for COVID-19 was recently made publicly available by the Canadian Drug Agency (formerly CADTH). Twenty-eight real world studies evaluating the impact of treatment were critically appraised and synthesized. Overall, CADTH concluded that the quality of these data was poor, with limited generalizability and high risk of bias. While many observational studies

reported some impact of nirmatrelvir/ritonavir on the risk of hospitalization from SARS-CoV-2, absolute risk reductions were small, with wide confidence intervals. Sub-group analyses, with the exception of those who were immunocompromised, yielded inconsistent results and questionable absolute impact. CADTH's recommendation to Canadian provinces and territories was to limit the widespread use of nirmatrelvir/ritonavir only to those with severe and moderate immunocompromise. Since the CADTH recommendations are largely based on real-world evidence from BC, the approach in this guide closely reflects current Canadian reimbursement policy and recommendations.

Evidence evaluating the impact of antivirals in patients over 50 years or those with comorbidities in the current pandemic context is still emerging. In the UK, the largest randomized controlled trial to date, [PANORAMIC](#), has closed enrolment on March 31, 2024, after recruiting thousands of such individuals into its nirmatrelvir/ritonavir arm. Preliminary results from this trial are expected to be published in the upcoming months. [CanTreatCOVID](#), a similarly designed trial being conducted in Canada, has so far enrolled over 500 patients and is expected to release interim results later this year.

Testing

A positive COVID-19 test result, either through a rapid antigen test (RAT) or through polymerase chain reaction (PCR) continues to be required for diagnostic purposes prior to prescribing antiviral medication. Since SARS-COV-2 is currently responsible for the minority of respiratory infections, and the differential includes a variety of pathogens such as influenza, respiratory syncytial virus (RSV), rhinovirus and many others, **a syndromic approach to treatment is not recommended. Rapid Antigen Tests (RATs)** remain the most common diagnostic modality in outpatients.

Any recent positive test result in patients in whom treatment is recommended is an acceptable microbiological diagnosis of COVID-19. **No confirmatory polymerase chain PCR test is required.** As incidence of COVID-19 decreases, the positive predictive value of a RAT falls dramatically. To increase its sensitivity, the RAT may be repeated daily within the antiviral treatment window, if negative. Despite convenience, RATs have other limitations, particularly low sensitivity in the first 24-28 hours of infection, and an inability to test for other pathogens.

The provincially funded RAT Program that provides tests free of charge to patients is ending in May 2025. Health care settings where these tests are given out such as pharmacies and clinics were informed that they can place orders for the remaining RATs until supplies last. Currently stocked tests do not expire until May 2026 and patients can continue to use RATs to access treatment. A final testing strategy once RATs are depleted or expire is pending.

RATs are not recommended in acute care settings and emergency departments. Patients at high risk of severe illness from viral respiratory pathogens that present for medical attention without a diagnosis are recommended to obtain a PCR test that includes influenza and RSV.

For patients who live in rural, remote or Indigenous communities, the health care provider may suggest PCR-based testing or other investigations based on their clinical evaluation. Offering PCR-based COVID-19 testing or a more comprehensive clinical investigation might be appropriate due to barriers to accessing health

services Indigenous people might experience, such as geographical remoteness or systemic racism. For full guidance on Testing in Remote, Rural and Indigenous Communities, [click here](#).

Symptoms and Symptom Progression

COVID-19 is a clinical illness and not a positive microbiological test, that requires an assessment of symptoms irrespective of satisfying other recommendations for treatment. Patients offered treatment should be **appreciably symptomatic from COVID 19 or have a non-reassuring clinical presentation and trajectory**.

Mildly ill patients are individuals who have upper respiratory symptoms that resemble a cold such as nasal congestion, runny nose, sore throat and headache often improve on their own without treatment. *A great deal of case-by-case clinical judgment is required to discern whether mild symptoms warrant treatment. In equivocal cases, a 24-48 hour follow-up/observation period is reasonable if still within the treatment window.*

Moderately ill patients who have systemic symptoms (high fever, myalgia, flu-like illness, gastrointestinal symptoms) and lower respiratory disease (increased work of breathing, dyspnea, abnormal chest imaging) have a higher risk of progression to severe disease.

A non-reassuring presentation is a clinical status that concerns the health care provider. For example, a patient post haematological stem cell transplantation may only have a low-grade fever; however, this is non-reassuring to their oncology team.

Illness trajectory helps establish the progression of COVID-19. Patients who are visibly deteriorating are more likely to become severely ill. *Treatment is unlikely to benefit those who are mildly ill and who are clearly improving on their own. Treatment should not be given to asymptomatic or minimally symptomatic patients.*

Symptom Window

Symptom windows vary with each therapeutic agent and follow study inclusion criteria. **Remdesivir should be given within 7 days of symptom onset** whereas for **oral antivirals should be given within 5 days**. *It is appropriate to allow the addition of adequate time for drug delivery of medication for those living in remote and rural communities.* Patients who are in highest risk category who have passed the 5-day mark but are within the 7-day treatment window and would not be referred for remdesivir solely based on its longer treatment window. They can be prescribed nirmatrelvir/ritonavir within 7 days of symptom onset.

In clinical trials, viral loads decreased from the nasopharynx by 1000's-fold during treatment regardless of the receipt of active treatment or placebo. Furthermore, most patients produced antibodies shortly after becoming infected and had robust cellular immunity responses. *There is little clinical rationale for extending the treatment window past 7 days.*

Patients who have prolonged symptoms or protracted illness may require a clinical assessment and work-up to rule out other responsible causes, including post-COVID condition (long COVID). The clinical benefit of antivirals is not known if they are prescribed later in the illness course.

Practical Prescribing and Coverage Considerations

Treatment can be prescribed by any physician or nurse practitioner in BC with a license to prescribe schedule I drugs. Unlike in other provinces, nirmatrelvir/ritonavir cannot be currently prescribed by community pharmacists and is not part of the pharmacy prescribing program for Minor Ailments and Contraception (MACs).

Nirmatrelvir/ritonavir can be prescribed using a [Paxlovid prescription](#), also available via E-forms. This is helpful but not mandatory.

Patients who are unattached, or who cannot see a prescriber in a timely manner can continue to self-refer to the COVID Assessment and Treatment eTeam (CATE), operated through services BC. Patients can call 811 to be connected, or access a [self-screener online](#) (or by calling 1-888-COVID19 if they'd rather speak to a Service BC service agent) to see if antivirals are recommended based on the above.

Nirmatrelvir/ritonavir is covered under [Plan Z](#) (Assurance Plan). This is a PharmaCare plan that does not require the typical income-based deductible to be paid by patients with MSP coverage and provides medication at no cost to patients. Remdesivir is fully reimbursed by hospitals.

Hospitalized Patients

Patients hospitalized for other reasons and are mildly-moderately ill with COVID-19 can be considered for treatment according to the recommendations herein. Please see the Inpatient Treatment Algorithm.

Most patients admitted to the hospital are incidentally diagnosed or are part of nosocomial outbreaks. As with all mild-moderately ill patients offered treatment, patients in the hospital need to be appreciably symptomatic, have a positive COVID-19 test, be assessed for contraindications and drug-drug interactions, and be offered treatment based on their risk of progression to severe disease. Even though patients are already hospitalized, the goal of such therapy is still the progression of COVID-19 to require hospital-level care for COVID-19, namely supplemental oxygen, steroids and baricitinib.

The treatment recommendations in this guide applies equally to all patients regardless of their location, including hospitalized patients. Nirmatrelvir/ritonavir OR remdesivir can be given to patients in whom treatment is recommended; the choice of agent depends on drug-drug interactions, contraindications and other considerations such as predicted length of hospital stay and IV access.

Post Exposure Prophylaxis (PEP)

Post Exposure Prophylaxis (PEP) with various COVID-19 therapeutics has been an active area of research; however, data from randomized controlled trials thus far have been negative.

Nirmatrelvir/ritonavir was evaluated in a manufacturer-sponsored RCT called [EPIC-PEP](#). This trial enrolled 2954 household contacts of symptomatic COVID cases, 2/3 of whom were deemed high risk for hospitalization or death. The development of symptomatic COVID-19 at day 28 was no different between

groups, with 2.6% vs. 2.4% vs. 3.9% in the placebo group experiencing the primary endpoint, for an RR of 0.7 p=0.2. In the high-risk groups (those with comorbidities), the rates were 2.4%, 2.6% and 3.4%, with a p-value of 0.67. Because of the negative results from EPIC-PEP, no jurisdiction employs this strategy, and no real-world data are available. Guidelines like from the NIH recommend against post-exposure prophylaxis. (<https://www.covid19treatmentguidelines.nih.gov/overview/prevention-of-sars-cov-2/>).

Contraindications and Drug-drug Interactions

Nirmatrelvir/ritonavir should not be prescribed to patients with hypersensitivity to ritonavir or other protease inhibitors. Nirmatrelvir/ritonavir is also contraindicated in in end-stage liver disease (Child-Pugh C). Patients with hepatitis B and C or HIV infection may benefit from Specialist Consultation (e.g., Infectious Diseases, HIV Specialist) especially due to drug-drug interactions.

Canadian nirmatrelvir/ritonavir labelling does not recommend administration in end-stage renal disease (eGFR <30ml/min) or dialysis. However, as per feedback from consultation with BC nephrology experts and careful review of the literature, nirmatrelvir/ritonavir may be used with renal dose adjustments. This strategy has also been approved in [other jurisdictions](#). Patients without known renal disease can be prescribed full dose nirmatrelvir/ritonavir without ordering baseline creatinine, and in those with reduced renal function, the most recent SCr can guide treatment decisions. Boarder-line eGFR (e.g., 28ml/min) should be assessed using clinical judgment; little risk exists by choosing either dosing.

Some drug-drug interactions contraindicate the co-administration of nirmatrelvir-ritonavir, but many can be held or managed. Contraindicated drugs include amiodarone, apixaban and rivaroxaban, certain antipsychotics like clozapine, midazolam and triazolam, as well as illicit drugs especially fentanyl and methamphetamine (see [Practice Tool: Drug Interactions and Contraindications](#)). Drug interactions must be verified, and a management plan must be in place before prescribing.

The most comprehensive resource for DDI assessment with nirmatrelvir/ritonavir is available from the University of Liverpool at <https://www.covid19-druginteractions.org/checker>.

The Canadian nirmatrelvir/ritonavir labelling does not include pediatrics and pregnancy as an indication. In the US, the FDA approved nirmatrelvir/ritonavir for kids 12 years and older weighing 40kgs or more. Various experts such as the US Society of Maternal-Fetal Medicine state that nirmatrelvir/ritonavir is safe in pregnancy, as with other protease inhibitors. Expert consultation is recommended.

Remdesivir is contraindicated in those with demonstrated hypersensitivity to the product or its ingredients. The monograph has been recently updated approving remdesivir in end-stage renal disease without dose adjustments. However, BC nephrology experts and pharmacokinetic data support dose-adjusted remdesivir by increasing the dosing interval to q48-72 hours. This dosing allows for administration of remdesivir post-dialysis on dialysis days and alleviates some of the high administrative burden and drug costs.

Remdesivir should not be used in patients with ALT ≥ 5 times the ULN. The pharmacokinetics and safety of remdesivir in severe hepatic impairment have not been evaluated; expert consultation is recommended. While pregnancy and paediatric considerations are not part of the Canadian labelling, remdesivir has

approval for children age ≥ 12 years weighing ≥ 40 kg in the US and has been given to pregnant women in independent studies. Specialty consultation is recommended for these populations.

Pregnancy, Breastfeeding and Pre-Conception

Pregnancy is a risk factor for hospitalization, and pregnant women have 3 times the odds of hospitalization in BC compared to age-matched non-pregnant women. Vaccination in this population is also lower than age-matched cohorts. However, pregnant persons are young, and most do not have co-morbidities. As such the absolute risk of hospitalization in a pregnant person is still below the treatment threshold.

Currently available therapies have not been evaluated in pregnancy or breastfeeding. The Reproductive Infectious Disease and Maternal Fetal Medicine COVID-19 working group would potentially consider remdesivir for use in pregnant or breastfeeding women if they otherwise meet the above-mentioned treatment criteria (e.g., immunocompromise). Nirmatrelvir/ritonavir may also be acceptable due to familiarity and comfort with prescribing protease inhibitors to this population. Animal studies have not demonstrated a significant risk to the fetus from all three drugs. Prescribers may consult Reproductive Infectious Disease on call at BCCW if prescribing COVID-19 therapy, especially nirmatrelvir/ritonavir in pregnancy in high-risk women, or for advice during breastfeeding.

It is unknown whether COVID-19 therapies impact fertility. Patients are encouraged to use protection while taking these medications. Those on oral contraceptives should use a backup method when taking nirmatrelvir/r due to drug interactions leading to lower plasma estrogen levels, decreasing its efficacy in preventing pregnancy.

Pediatrics

Nirmatrelvir/ritonavir is not approved for pediatric use in Canada (but is in the US), and remdesivir is not approved in children with mild-moderate COVID-19 in Canada (but is in the US). The following statement regarding pediatric therapy has been developed in collaboration with experts from BCCH:

Pediatric patients with immunocompromise are generally considered at lower risk of developing severe COVID-19 illness and requiring hospitalizations compared to adults with immune compromise. The risk of severe COVID disease in immunocompromised children appears to be related to underlying comorbidities rather than immune suppression. Immunocompromised children may present with atypical signs and symptoms of COVID-19 that can fluctuate rapidly between being asymptomatic and having mild to moderate symptoms. Information on COVID-19 vaccine immunogenicity in children with immune compromise is currently limited.

In consultation with pediatric infectious diseases and appropriate subspecialist, treatment should be considered for COVID 19 positive immunosuppressed children 12 years or older and minimum 40kg with mild to moderate COVID-19 symptoms not requiring hospitalization who are:

- Solid organ transplant recipients
- Hematopoietic stem cell/bone marrow transplant recipients within the past 2 years and/or are currently receiving immunosuppression

- Immunosuppressed due to primary immunodeficiency or due to iatrogenic causes
- Have been otherwise classified as extremely clinically vulnerable due to immunosuppression

AND

- Have another major chronic condition/comorbidity putting them at risk of severe COVID-19, especially significant lung disease (e.g., lung transplant recipients, lung GVHD, obstructive lung disease). Being unvaccinated or partially vaccinated is a risk factor for severe COVID-19 disease, bearing in mind that some fully vaccinated children with immune compromise also may not generate vaccine immune response.

The choice of agent will depend on an individualized risk-benefit assessment of the available therapies. Children with immunocompromise and no major comorbidities are unlikely to develop severe COVID-19 disease. The benefit of providing treatment in these cases is likely very small.

Ultimately, decisions around the use of remdesivir or sotrovimab should be made on a case-by-case basis, weighing lack of RCT-level data in children, off-label use and the potential benefit of treatment. Clinicians are encouraged to discuss cases with the Pediatric Infectious Diseases physician on call at BC Children's Hospital. If IV therapy is pursued, infusions can be arranged at BC Children's hospital through the patient's BC Children's Main Responsible Physician/Service, per hospital protocol. For those patients outside the vicinity of BC Children's hospital, arrangements will need to be made through the local health authority at an available infusion site.

Rebounds, Re-infections and Retreatment

Rebounds

A rebound, also known as a relapse, is defined as a COVID-19 infection which was treated (mainly with nirmatrelvir/ritonavir) where there was proven clearance of the SARS-COV-2 virus by a negative test and symptom improvement, but where symptoms then returned or worsened, followed by a subsequent positive SARS-COV-2 test. Rebounds are not frequently diagnosed because current guidance does not recommend a test of cure, especially since patients can shed the virus for weeks after recovery and have an undulating symptom trajectory. It has been speculated that treatment with nirmatrelvir/ritonavir causes rebounds because it suppresses the virus beyond detectable levels without complete clearance. Once the 5-day course is completed, the virus replicates again, causing a rebound of illness. However, rebounds have since been shown to occur irrespective of whether treatment is given and are estimated to affect approximately 2% of patients. In a recent meta-analysis, the overall OR of rebound among COVID-19 patients taking nirmatrelvir/ritonavir vs. control group was 0.99 (95% CI, 0.28–3.57; $p=0.99$), showing no association between treatment and rebounds. Patients with COVID-19 should be counselled that rebounds may occur but are not linked to treatment, and post-treatment testing or test of cure should be discouraged.

Re-infections

Re-infection is defined as a COVID-19 infection after complete recovery from a prior infection and usually occurs with a different variant of concern. Re-infections in BC have been documented by PCR as early as 8

weeks prior to the original infection and became common during the Omicron waves despite the protection the previous infection confers. [Studies](#) show that re-infection rates in a highly vaccinated population are highest in 18–29-year-olds (~15%) and about 10% in the general population.

Retreatment

The [CDC](#) does not recommend routine re-treatments of rebounds. Rebounds are generally milder than the index infection, and symptoms resolve quickly without re-treatment. Case series of rebounds, however, have been in already low risk individuals who would not have been eligible for treatment in BC. The CTC recommends that patients who meet treatment eligibility and rebound be reassessed on the basis of their symptoms and symptom trajectory. Those with symptoms that are milder than the initial infection or those that are improving rapidly should not be offered re-treatment. Re-treatment with nirmatrelvir/ritonavir can be considered in those with significant symptoms or rapidly progressing illness. Another 5-day course should be used; no evidence supports longer courses of treatment, although the manufacturer is currently investigating a 10-day course.

Re-infections should be assessed and treated as new infections. Patient's eligibility criteria should be re-assessed, and risk re-calculated considering previous infection in the risk scoring. Symptoms and symptom trajectory should continue to play a key role in determining whether another course of treatment is offered.

So far, a few dozen patients in BC have received more than one course of nirmatrelvir/ritonavir. There have been no observable differences in outcomes between the first vs. the second course of nirmatrelvir/ritonavir, although a significant survival bias exists.