BC COVID THERAPEUTICS COMMITTEE (CTC)

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

November 2023 Update: Revised criteria for remdesivir eligibility in outpatients.

GENERAL INFORMATION

About this Guide

This practice guide provides eligibility criteria and 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 additional practice tools available separately. *See Toolkit #1 – Step-by-step Assessment for practical prescribing information.*

RECOMMENDATIONS

Eligibility for nirmatrelvir/ritonavir (Paxlovid):

- Immunocompromised individuals[1,2] and those with high-risk conditions[3] identified as Clinically Extremely Vulnerable Group 1[1], Group 2[2], and Group 3[3] **(CEV 1, CEV 2, and CEV 3), regardless of age, vaccine status** or previous infection. *(See also Practice Tool 2 – CEV Definitions).*
- Individuals with **TWO of the three** following risk factors:
  - **≥70 years** (≥ 60 years if Indigenous), AND/OR
  - **unvaccinated** or **under-vaccinated** as per Strong Recommendations by NACI^, AND/OR
  - have a **serious chronic medical condition***
- **Individuals residing in Long Term Care facilities** (see guidance statement below)

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1. CEV 1: severe immunocompromise due to, e.g., solid organ transplant, bone marrow or stem cell transplant, treatment for hematological malignancy, receiving anti-CD20 or B-cell depleting therapies
2. CEV 2: moderate immunocompromise due to e.g., receiving immunosuppressive agents, moderate-severe primary immunodeficiency, cancer treatment for solid tumors, advanced or untreated HIV
3. CEV 3: e.g., cystic fibrosis, severe asthma or COPD, diabetes requiring insulin, intellectual and developmental disabilities, rare blood disorders, dialysis, neurological conditions requiring Bi-PAP or chronic ventilation, cancer not captured above

^ National Advisory Committee on Immunization strongly recommends a primary two-dose series PLUS a subsequent dose (XBB or bivalent) in the last year for those ≥65 or with serious chronic conditions, which may be delayed 6 months post COVID-19 infection.

*Serious chronic medical conditions may include stroke, heart failure, heart disease, diabetes, kidney or liver disease, chronic lung disease like COPD or interstitial lung disease, neurological conditions. Some discretion can be used.

Therapy Recommendations
Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days (150/100mg PO BID x 5 days in eGFR 30-60 ml/min) **is recommended** within 5 days of symptom onset for patients with a non-reassuring symptom presentation and trajectory who are at an increased risk for hospitalization or progression to severe COVID-19 as defined by the eligibility criteria. NOTES: The eligibility criteria above apply to outpatients, patients presenting to the emergency department or hospitalized patients who have COVID-19 of mild-moderate severity. See below for eligibility criteria for residents of long-term care facilities. Strong clinical judgment assessing symptoms and symptom trajectory is particularly important in immunocompromised patients. 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.
Nirmatrelvir/ritonavir **may be considered** in patients who reside in Long Term Care (LTC) facilities. There are a lack of data supporting the efficacy and safety of nirmatrelvir/ritonavir in patients residing in LTC facilities. Treatment may be given depending on patient's clinical presentation, symptom trajectory, risk factors for progression to severe disease, goals of care, presence of drug-drug interactions and tolerance of potential adverse effects. Nirmatrelvir/ritonavir should not be used for post-exposure prophylaxis as data for this indication have been negative.

If nirmatrelvir/ritonavir cannot be given to eligible patients due to drug-drug interactions or contraindications (See Practice Tool 3 – Drug Interactions and Contraindications),
 	
Remdesivir 200mg IV on day 1, followed by 100mg IV on days 2 and 3 (200mg IV on day 1, followed by 100mg IV 48-72 hours later in eGFR less than 30ml/min) **is recommended** within 7 days of symptom onset as an alternative to nirmatrelvir/ritonavir to outpatients at highest risk of progression to severe disease, i.e.,:
• Immunocompromised individuals identified as Clinically Extremely Vulnerable group 1 **(CEV 1)** regardless of age, vaccine status or previous infection.
• Clinical Extremely Vulnerable patients in groups 2 and 3 (**CEV 2/3) aged 60 years or older**, or
• Under **extenuating circumstances**, (clinical judgment required), patients who have NOT had a COVID-19 vaccine or COVID-19 infection in the last year who are:
  ○ CEV 2/3 less than 60 years, or
  ○ Elderly 70 years or older with 3 or more chronic conditions
NOTES:
Outpatients with the highest risk of hospitalization are currently being prioritized and offered treatment with remdesivir due to operational constraints and unclear benefit in lower risk individuals.
 	
Inpatients with mild-moderate COVID-19 are at higher risk of progression to severe disease than outpatients, and they may be offered remdesivir in accordance with the nirmatrelvir/ritonavir eligibility criteria if drug-drug interactions or contraindications are present.

Sotrovimab 500mg IV X 1 dose has reduced efficacy against all Omicron variants, although it may retain some activity. Real-world evidence shows limited efficacy against the BA 1. and BA. 2 variants of concern (VoCs) in immunocompromised or non-immune individuals, which may predict its performance against most currently circulating VoCs based on binding studies. Sotrovimab has unknown clinical efficacy against many currently circulating VoCs (e.g., XBB 1.5 and EG.5) where a reduction in binding, but not complete resistance, is seen. If sotrovimab is used in cases where remdesivir or nirmatrelvir/ritonavir cannot be used, patient disclosure of risks and benefits in consideration of individual circumstances (clinical and immune status, patient values, logistics) is necessary. The convenience of single dose sotrovimab should not be the primary indication for use.

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 600mg IM x 1 dose 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 likely ineffective against many currently circulating VoCs including BA. 4.6, BF. 7, BA. 2.75.2, BQ 1, BQ 1.1 and XBB where 300-1000-fold reductions in binding are seen.

Molnupiravir 800mg PO BID x 5 days is not routinely 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.

PRACTICAL CONSIDERATIONS

Risk Assessment

Single variable criteria (e.g., age only) identify patients with a wide range of risks and are an imprecise way to determine who is at high risk of severe COVID-19 and would benefit from treatment. Unless patients are Clinically Extremely Vulnerable (CEV), real-world data show that they require at least two risk factors to have a clinically meaningfully increased risk of hospitalization from COVID-19 and therefore derive a reasonable benefit from treatment.

Age: Age is the single most powerful predictor of hospitalization and death; an 80-year-old patient with COVID-19 has 28 times greater odds of requiring hospitalization than a patient who is 18. Patients over 70, even if vaccinated, experience significant hospitalization rates despite the decreased likelihood in the Omicron variant wave especially if it is their first COVID-19 infection, whereas individuals younger than 50 years have a hospitalization rate of <1% even if unimmunized (see recent BC data). The age cut-off of 70 years was chosen as there is a strong inflection point with respect to the risk of hospitalization. The age cut-off for Indigenous patients is lower, set at 60 years, which mirrors COVID-19 vaccine booster recommendations in BC.

Vaccine Status: The National Advisory Committee on Immunizations (NACI) COVID-19 Immunization Guidelines include recommendations regarding the optimal vaccination strategies for COVID-19, which are adopted in BC. These recommendations consider the complexities of vaccine waning and hybrid immunity. Recommendations are presented as "Strong Recommendations" (worded as "should be offered") where the evidence of benefit for a vaccine is convincing, and "Discretionary Recommendations" (worded as "may be offered") where there are limited data or an unclear clinical benefit.

Currently, NACI strongly recommends the following immunization strategy, which is used herein to define what is considered fully or optimally vaccinated:

- A primary two-dose mRNA vaccine series for all adults.
- A three-dose primary series for those who are immunocompromised (CEV 1 and 2).
- A "Fall Booster" for those ≥ 65 years and older or those < 65 who have serious chronic medical conditions
- The Fall Booster may be delayed for up to 6 months in case of a COVID-19 infection
    - In the Fall of 2023, an XBB 1.5 vaccine has replaced the previous bivalent vaccine and is no longer referred to as a "booster"

Patients who have never received a COVID-19 vaccination are considered unvaccinated. Patients who are not vaccinated in accordance with NACI's strong recommendations would be considered under-vaccinated. When assessing vaccine status for treatment eligibility, *a lack of a vaccine dose in the last year (and a lack of infection which could delay the dose) is a good gauge of under-vaccination* since the presence of another risk factor (older age or chronic conditions) is required for treatment, which is also a risk factor where a booster would be recommended.

Chronic Conditions: Real-world evidence shows that serious medical chronic conditions are the most strongly associated with the risk of hospitalization from COVID-19. In BC, the most common conditions when nirmatrelvir/ritonavir was prescribed were hypertension, dyslipidemia and benign prostatic hypertrophy, which are not associated with an increased risk of progression to severe disease. Non-CEV-defining conditions that are significant risk factors are similar to those defined by NACI, and include:

- Stroke
- Heart failure or heart disease (myocardial infarction, angina)
- Diabetes
- Kidney disease
- Liver disease
- Chronic lung disease such as COPD, bronchiectasis, interstitial lung disease
- Neurological conditions such as Parkinson's disease

The patient requires the presence of any ONE of these serious chronic medical conditions. The prescriber can use discretion when determining the significance of the severity of the comorbidity.

Other considerations: The risk models/thermal map below are still accurate in estimating the risk of progression to severe COVID-19. These models may be used to aid decision making or when assessing for the appropriateness of remdesivir**. Remdesivir can be offered to patients with contraindications to nirmatrelvir/ritonavir who have a ≥ 5% risk of hospitalization from COVID-19** (dark yellow and red on the thermal map).

Testing

BC is continuing to rely on the federally acquired rapid antigen tests (RATs) available at pharmacies. As this program comes to a gradual end, the testing strategy in BC will change, and this guideline will be updated to reflect this.

Any recent positive test result in patients who are eligible for treatment is acceptable as a part of making the diagnosis of COVID-19. **At this time, the Provincial test-to-treat strategy is emphasizing Rapid Antigen Tests (RATs) as the first-line testing method for outpatient patients with symptoms consistent with COVID-19 who are candidates for therapy. No confirmatory Polymerase Chain Reaction (PCR) test is required. To increase the sensitivity of the RAT, the test may be repeated daily within the antiviral treatment window, if negative.**

Current testing guidelines issued by the BCCDC in collaboration with the CTC focus on testing using Rapid Antigen Tests for treatment purposes. An evaluation of patients who accessed outpatient therapeutics in BC showed that 88% of all tests that led to a prescription for a COVID therapy in outpatients were based on a RAT. RATs offer a low barrier to access as they are widely available free of charge at local pharmacies, can be self-administered by the patients. Rapid antigen tests may be especially important for people living in communities with limited health services, such as rural, remote, and isolated or Indigenous communities, work camps, and Indigenous people living in urban settings. RATs have important limitations such as the lack of quality control over current and emerging VoCs, as well as lower sensitivity.

Patients eligible for treatment should be encouraged to get tested if symptomatic. If the test is negative and the patient continues to feel sick, they can be directed to repeat the test in 24 hours. **As long as they are within 5 days of symptoms starting and clinically stable, they may repeat the test every day to the 5th day.**

Patients who continue to test negative but in whom the clinical suspicion is high or are concerned about the severity or trajectory of their symptoms should contact their healthcare provider to obtain a nucleic acid amplification test (NAAT). In such cases a work-up may be required, including additional testing (for COVID-19, other infections and/or other illnesses) based on their clinical evaluation.

The CTC and BCCDC are currently in the midst of publishing testing guidance for respiratory viral pathogens for the 2023-24 respiratory season, including how and when to order a NAAT. Please check back shortly for an updated link to this document.

Evidence:

Studies show that RATs offer excellent specificity but lower laboratory sensitivity than PCR methods. For example, a Cochrane review cited that while the specificity of RATs in individuals was over 99%, on average, the sensitivity was 82% if patients tested within the first week of symptoms. The sensitivity of RATs, when compared against PCR tests, increases under specific circumstances:

- Symptomatic patients are more likely to have a true positive RAT over those without symptoms
- Performing a test on day 3 or later since symptom onset as opposed to on days 1 or 2
- Having higher viral loads, as seen in patients who have greater vaccine escape, are more symptomatic or are 48 hours or more into their illness
- Performing serial RATs at regular intervals (e.g., every 24-48 hours).

Various studies have evaluated serial RATs in symptomatic patients for their diagnostic accuracy. The largest study to-date, the Test Us at Home trial, showed that in patients who were pre-symptomatic but went on to develop symptoms of COVID-19, performing a self-administered RAT three times over a 48 hour interval produced an aggregate sensitivity of 93.4% (95% CI: 89.1-96.1%). Testing once on the day symptoms appeared had a sensitivity of 59.6%, which increased to 92.3% after a single repeated test (total of 2 tests within a 48-hour period). Testing asymptomatic patients, even in a serial fashion, produced a sensitivity of 56.4%. This study has led to an FDA Guidance Update recommending serial RAT testing for all symptomatic individuals as the optimal testing strategy to ensure maximum sensitivity. To ensure the quickest diagnosis possible through retesting, considering the 5-day treatment window, the CTC and the Province recommend retesting 24 hours after a negative RAT, instead of a longer interval between tests.

Testing and Treatment Evidence

Currently, no studies compare the impact of different testing strategies (RAT vs. PCR) on treatment outcomes (e.g., hospitalization or death). While a positive PCR test is often a part of the inclusion criteria of randomized controlled trials of COVID-19 therapeutics, most real-world studies describe a mainly RAT-based approach through which COVID-19 was diagnosed and treated. As long as patients initiate treatment within the treatment window (5 days for nirmatrelvir/ritonavir and 7 days for remdesivir) landmark trials of nirmatrelvir/ritonavir and remdesivir show no difference in treatment outcomes based on the day the patient started therapy. For example, patients who started nirmatrelvir/ritonavir within 3 days of symptom onset had the same reduction in hospitalization as patients who initiated treatment within 5 days (0.7% vs. 6.5% and 0.8% vs. 6.3%). Very few patients initiate treatment on the first day of symptom onset, where PCR testing may have a sensitivity advantage over a single RAT test.

Practical Considerations for assessing validity of a Rapid Antigen Test:

- Ensure the test was done recently and that it is positive
- For patients who test positive via a RAT, verify how the test was done and how did the result present.
- While RATs have excellent clinical specificity as they are unlikely to pick up SARS-COV-2 virus in those who have recently recovered from COVID, are chronic shedders or have subclinical viral loads, false positives can occur. Potential causes for false positive results may include other respiratory viruses and reactions with certain foods or liquids.

- The pre-test likelihood of COVID-19 infection may be influenced by known contact with COVID-19 cases, symptoms compatible with COVID-19, and the prevalence of disease in the community. The table below provides the positive predictive value for a single RAT test with 98% specificity and 80% sensitivity (similar to most RATs performed in symptomatic patients) for a range of pre-test probability of infection from 0.01 to 0.15.

Pre-test probability of infection	Positive Predictive Value
0.01	0.29
0.05	0.68
0.1	0.82
0.15	0.89

Epidemiologically linked cases (e.g., household contacts of those who test positive) who have not been confirmed via COVID-19 testing should not be offered treatment.

Indications for a NAAT Test

NAAT testing will continue to be performed on patients within acute care settings, including hospitalized patients and those presenting to the emergency department, or to investigate an outbreak. A NAAT is required for genomic characterization of the virus (aka Variants of Concern typing) for surveillance purposes, which also informs the activity of monoclonal antibody treatments. NAATs are also used when there is a need to diagnose influenza (these tests are done together), or when patients eligible for treatment present to a health care provider without a diagnosis after having tested negative via a RAT.

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.

NAAT testing may also be ordered in the community for treatment purposes at the discretion of the primary care provider. Scenarios where NAAT testing may be appropriate include:

- High-risk patients who test negative despite performing a RATs, especially if not improving
- Patients with a very high-level of suspicion (e.g., symptomatic with a household contact) who test negative despite serial RATs
- Patients who have symptoms of severe disease who will have COVID-19 therapy (e.g., supplemental oxygen, dexamethasone) delivered outside of an acute care setting

Types of NAAT tests available vary (e.g., saline gargle tests, NP swabs) and are subject to change. Healthcare providers wishing to order NAAT testing should consult their local Health Authority resources for up-to-date guidance. As NAAT testing results may take 24 hours or more, patients for whom treatment is indicated can also perform serial RATs while awaiting NAAT results if the turn-around-time exceeds one day.

Resistance to Therapeutics and Variants of Concern

While viruses exhibiting resistance to antivirals have been engineered in-vitro, there have thus far been no documented cases of resistance to nirmatrelvir or remdesivir isolated clinically. Resistance to monoclonal antibodies, however, is common, and nearly all circulating variants of concern in BC show either reduced susceptibility to mAbs, or complete resistance. Resistance is unpredictable and binding affinity varies greatly within the BA.5 sublineage of Omicron and among recombinant variants. Furthermore, VoCs circulating in BC fluctuate greatly weekly, offering limited visibility.

As of August 2023, EG.5, which carries the same spike amino acid profile as XBB 1.5 is the predominant variant circulating in BC. A current breakdown of VoC in Canada is found here. The table below depicts the decrease in binding to tixagevimab/cilgavimab and sotrovimab.

Variant of Concern	% of total VoCs as of August 27, 2023	Fold reduced neutralizing susceptibility	
		Tixagevimab/cilgavimab	Sotrovimab
EG.5	38.5%	476	18
XBB 1.9	29.7%	476	18
XBB 1.16	12.9%	488	5
XBB 1.5	8.5%	>1000	18
XBB 2.3	8.5%	738	14
Other		Variable	Variable

Sotrovimab: Reasonable susceptibility and clinical efficacy are expected for sotrovimab at a 23-fold reduction in binding based on the Open Safely study. The study included CEV-1- and CEV-2-type patients infected with the BA. 2 VoC, which has the same degree of reduced neutralizing susceptibility as most BA. 5 variants. This high-risk population's hospitalization rate in this RCT was 0.95% vs. 2% compared to an active control (molnupiravir). At this cut-off, most currently circulating VoC are likely susceptible to sotrovimab.

Tixagevimab/cilgavimab: No real-world clinical data characterizes the performance of tixagevimab/cilgavimab for treatment against any Omicron variant. Data for prophylaxis suggest reasonable neutralization at a 50-fold reduction in binding seen against BA. 1. At this cut-off, approximately 95% of VoCs in BC are highly resistant to tixagevimab/cilgavimab.

Symptoms and Symptom Progression

Patients offered treatment should be **appreciably symptomatic from COVID 19 or have a non-reassuring clinical presentation.** Patients who are **moderately ill,** i.e., showing evidence of lower respiratory disease during clinical assessment or imaging and who have decreased oxygen saturation (but still ≥94% on room air) *are most likely to progress to severe illness requiring supplemental oxygen and can be offered therapy.*

Mild illness, i.e., individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have, dyspnea, increased work of breathing or abnormal chest imaging can progress to severe

illness, especially if those symptoms are profound, or exist in combination. Flu-like symptoms such as fever and diffuse myalgia are indicative of systemic illness and are associated with a higher risk of illness progression. *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 period is reasonable if still within the treatment window.*

A non-reassuring presentation is a clinical status that concerns the health care provider. For example, a CEV-1 cancer patient 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 but are within the 7-day treatment window and would be referred for remdesivir solely based on its longer treatment window can be prescribed nitmatrelvir/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 exogenous antibodies do not confer additional benefit. *There is little clinical rationale for extending the treatment window past 7 days.*

Patients who have had prolonged symptoms or more or protracted illness despite recently testing positive for COVID-19 may require a clinical assessment of the illness trajectory to rule out other causes responsible for their symptoms. Patients are encouraged to get tested as soon as possible after COVID symptoms appear to avoid conflating persistent symptoms with COVID-19 infection.

Hospitalized Patients

Patients hospitalized for other reasons and are mildly-moderately ill with COVID-19 can be considered for treatment if they meet the eligibility criteria for Nirmatlervir/ritonavir. Many patients admitted to the hospital are incidentally diagnosed or are part of nosocomial outbreaks and are offered testing with very low thresholds that often do not warrant treatment. As with all mild-moderately ill patients offered treatment, patients in the hospital need to be appreciably symptomatic, have a valid 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 guidance in this guide applies equally to all patients regardless of their location, including hospitalized patients. Nirmatlervir/ritonavir OR remdesivir can be given for patients who meet the eligibility criteria; the choice of agent depends on drug-drug interactions, contraindications and other considerations such as predicted length of hospital stay an 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. Study participants were excluded if they had a COVID-19 infection or vaccination in the 6 months prior to screening. The VoCs seen in the trial included mainly Delta, which had a much higher propensity for causing severe disease; however, the Omicron VoC was also seen in the latter part of the study. Participants were randomized to Paxlovid for 5 or 10 days given post-exposure, or placebo. 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. Hospitalization and death were evaluated as a secondary endpoint. There were none in the treatment groups and 1 patient in the placebo group.

Because of the negative results from EPIC-PEP, no jurisdiction employs this strategy, and no real-world data are available. Despite showing promise before vaccination was available, evidence for PEP with other therapeutics is largely negative, and as such, guidelines like from the NIH recommend against post-exposure prophylaxis. (https://www.covid19treatmentguidelines.nih.gov/overview/prevention-of-sars-cov-2/).

PEP also poses safety concerns, particularly for patients residing in long-term care who are at risk of COVID-19 during outbreaks but have many drug-drug interactions that complicate the widespread use of nirmatrelvir/ritonavir. For example, a recent evaluation from Providence Health Care showed that 63% of residents had limiting DDIs with nirmatrelvir/ritonavir, with 34% being with anticoagulants and 51% with antipsychotics.

Because of safety risks combined with evidence demonstrating **no benefit** of Paxlovid for PEP (EPIC-PEP trial), the use of nirmatrelvir/ritonavir for **PEP** is currently **not recommended in any setting**.

Contraindications

Nirmatrelvir/ritonavir should not be used in end-stage liver disease (Child-Pugh C). Patients with hepatitis B and C or HIV infection, regardless of treatment status, may benefit from Specialist Consultation (e.g., Infectious Diseases, HIV Specialist). Treatment should not be withheld or delayed due to these conditions. Many drug-drug interactions contraindicate the co-administration of nirmatrelvir-ritonavir, but some 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 #3: Drug Interactions and Contraindications).* Patients with

hypersensitivity to ritonavir or other protease inhibitors should not be prescribed nirmatrelvir/ritonavir. **Drug interactions must be verified, and a management plan must be in place before prescribing. If drug-drug interactions pose safety concerns, treatment can be forgone, especially in those with a slightly increased hospitalization risk.**

Nirmatrelvir/ritonavir has not been clinically evaluated in patients with eGFRs < 30ml/min, although pharmacokinetic studies show that it is not nephrotoxic and can likely be adjusted accordingly in those with end-stage renal disease or on dialysis. The manufacturer is conducting a small trial in patients with eGFRs less than 30ml/min; safety and efficacy data are forthcoming. According to BC nephrology experts, nirmatrelvir/ritonavir is thought to have a limited role in patients with end-stage renal disease due to the extensive number of drug-drug interactions such patients experience and not because of renal disease itself. However, the drug is not considered dangerous in such patients, and a lack of recent serum creatinine should not contraindicate or delay its administration. Patients without known renal disease can be prescribed full-dose nirmatrelvir/ritonavir, 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 and does not usually contraindicate prescribing dose-reduced nirmatrelvir/ritonavir 150mg/100mg PO BID.

Remdesivir is contraindicated in those with demonstrated hypersensitivity to the product or its ingredients. While the monograph states that there are no data to support its use in eGFR < 30ml/min (due to the cyclodextrin component), numerous studies, including a yet-to-be-published RCT of >1000 patients conducted by Gilead support its safety in this population. (For a full operational review of remdesivir, including renal dosing, consult your health authority to obtain the CTC and CTRAWG memo regarding remdesivir operationalization). Remdesivir should not be used in patients with ALT ≥5 times the ULN. The pharmacokinetics and safety of remdesivir in 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 ≥ 40kgs in the US and has been given to pregnant women in independent studies. Specialty consultation is recommended for these populations.

Monoclonal Antibodies: Although they are rare, monoclonal antibodies like sotrovimab and tixagevimab/cilgavimab can cause hypersensitivity reactions and infusion/injection reactions.

Molnupiravir contraindications are not well articulated as the Canadian Monograph has not been published due to lack of Health Canada approval. This will be updated when known. Based on FDA data, molnupiravir will be contraindicated in pregnancy, breastfeeding, those trying to conceive, and pediatrics.

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 or unvaccinated). Nirmatrelvir/ritonavir may also be acceptable due to familiarity and comfort with prescribing protease inhibitors to this population. Sotrovimab is considered safe; however, this needs to be balanced against a potential loss of activity. 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.

Molnupiravir has been found to negatively impact fertility, embryonic development and pregnancy outcomes in animal studies and is contraindicated in pregnancy or in those with childbearing potential unable or unwilling to use protection.

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, and remdesivir is not approved in children with mild-moderate COVID-19 in Canada (but is in the US). Sotrovimab has pediatric approval but significantly loses neutralization capacity against BA.2 and may not be appropriate in very high-risk children. The following statement regarding pediatric therapy has been developed in collaboration with experts from BCCH:

Pediatric patients with immune compromise 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 of 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 (CEV 1 or 2)

AND

- Have another major chronic condition/comorbidity putting then 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 immune compromise 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.

Drug-Drug Interactions

Nirmatrelvir and ritonavir have significant drug-drug interactions, many of which contraindicate its use. Nirmatrelvir and ritonavir are potent inhibitors of CYP 3A4 and increase the concentration of many drugs metabolized by this enzyme. Nirmatrelvir/ritonavir is also contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

Some drug-drug interactions can be managed. For a comprehensive list of drug-drug interactions and management strategies see *Practice Tool #3: Drug Interactions and Contraindications*.

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

Remdesivir has no DDIs that contraindicate its treatment, except for chloroquine and hydroxychloroquine, which may reduce its antiviral efficacy. Strong CYP 3A4 inducers (e.g., phenytoin, rifampin, carbamazepine) may decrease the serum level of remdesivir, but this interaction's clinical relevance is not known.

Sotrovimab and tixagevimab/cilgavimab pose no significant drug-drug interactions.

Dosing

Nirmatrelvir/ritonavir is dosed at **nirmatrelvir/ritonavir 300/100mg PO BID x 5 days for those with eGFR > 60 ml/min.** It is supplied as a pre-packaged kit containing both products: 2 tablets of nirmatrelvir 150mg and 1 tablet of ritonavir 100mg per dose. The patient takes 3 tablets per dose, for a total of 30 tablets during the treatment course.

Patients with an **eGFR of 30-60 ml/min should take nirmatrelvir/ritonavir 150/100mg PO BID x 5 days,** or one nirmatrelvir 150mg tablet and one ritonavir 100mg tablet per dose. The second nirmatrelvir tablet should be removed from the kit from each dose by the dispensing pharmacist for the patient to avoid confusion and diversion.

Nirmatlervir/ritonavir has also been used in end-stage renal disease and dialysis, and further dose reductions are routinely recommended off-label in some jurisdictions such as Ontario. The CTC is currently working with nephrology stakeholders to determine if these practices should be implemented in BC.

Renal Dosing of remdesivir

Remdesivir for mild-moderate COVID-19 in patients with an **eGFR ≥ 30ml/min is dosed with a loading dose of 200mg IV on day 1, followed by 100mg IV on days 2 and 3.** *This dose differs from its dose in the monograph for severe COVID-19 infection.* Each vial contains remdesivir 100mg for a total of 4 vials per full treatment course. No dose adjustment is required for obesity or mild-moderate renal or liver impairment. Patients with renal disease who have an eGFR <30 ml/min can safely receive standard dosing; however based on known PK and limited clinical data, renal and COVID experts in BC agree that a renally adjusted dosing can be used to optimize operationalizing administration of infusions. Such patients can receive 200mg IV on day 1, followed by 100mg IV 48 hours later. Patients on hemodialysis can receive their dose during dialysis, and can receive their second dose 48-72 hours later depending on their hemodialysis schedule.

Sotrovimab is dosed at 500mg IV x 1 dose infused over 60 minutes. The manufacturer is currently evaluating the in-vivo efficacy of a 1000mg dose against different variant of concern, as such dose is likely to overcome the reduced neutralization capacity. A regulatory decision regarding the approval of this dose is forthcoming. No dose adjustments are required for obesity or mild-moderate renal or liver impairment. The drug is not recommended for IM use.

Tixagevimab/cilgavimab for treatment is dosed at 600mg, 300mg of each tixagevimab and cilgavimab. The two antibodies are supplied separately and are injected intramuscularly into the gluteal muscles as four 1.5mL IM injections (two 1.5mL injections each mAb). There are no dose adjustments for renal or liver impairment.

Patient Location

Patients with mild to moderate COVID-19 are usually outpatients recovering at home. However, many patients hospitalized for non-COVID reasons can also be offered treatment *(see Hospitalized Patients above).* All patients in Long-Term Care are eligible for treatment, with an understanding that IV therapeutics may not be able to be administered easily in LTC settings. Patients may also be offered treatment in Emergency Departments. With the exception of remdesivir eligibility criteria in outpatients, this guidance is not specific to any particular patient location.

This guide does not specify priority for patients in remote or rural areas; CTRAWG (a committee responsible for the equitable distribution of scarce drug resources) may prioritize different geographical areas if needed.

Additional time added to the patient's symptom window is clinically acceptable for drug transport to remote and rural areas.

Clinical Judgement

This guide should not replace clinical judgment. Patients who are technically eligible for treatment may not be good candidates due to clinical status, goals of care, or willingness to provide consent for treatment. These factors need to be considered with each patient assessment.

The current eligibility criteria are conservative, and the absolute risk of hospitalization depicted in thermal maps is overestimated due to a testing bias. There should be very few patients with a risk of <3% who should be offered treatment and are not captured in this guide; however, such decisions are again deferred to the treating clinician.

Rebounds, Re-infections and Retreatment

Rebounds

A rebound, also knowns 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.

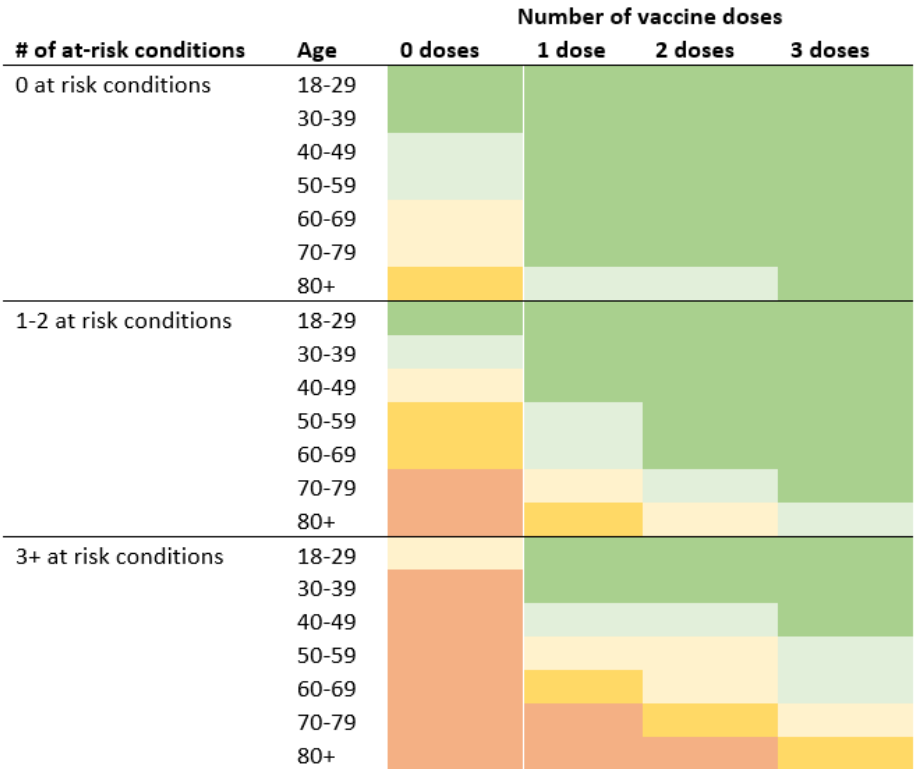
Re-infections should be assessed and treated as new infections. Patient's eligibility criteria should be re-assessed, and risk re-calculated considering previous infection in the risk scoring. Symptoms and symptom trajectory should continue to play a key role in determining whether another course of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

SUPPORTING EVIDENCE

Local Data and Risk Models

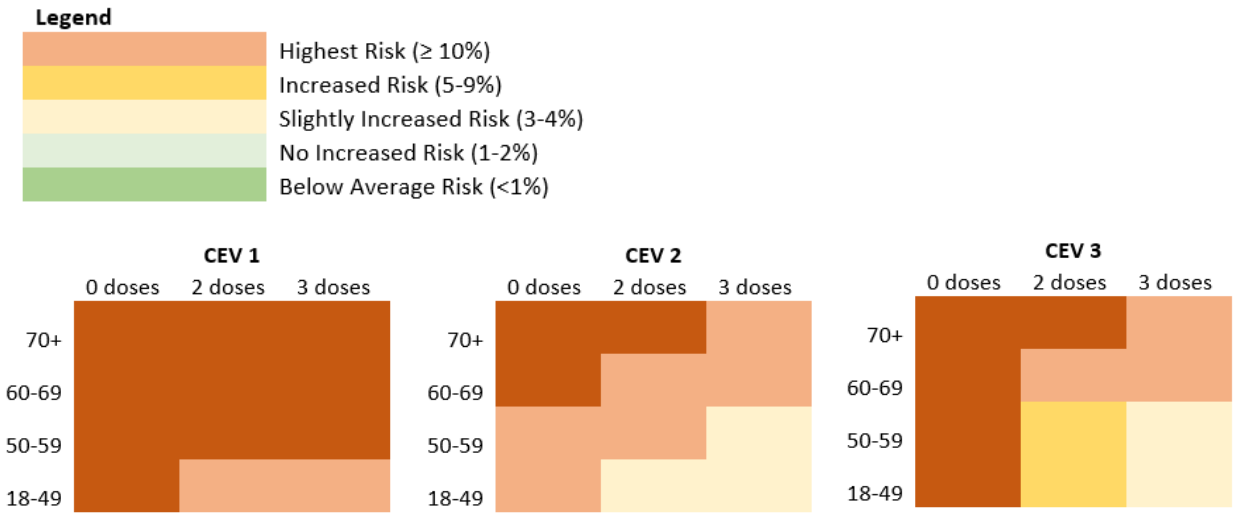
BC Study of Risk of Hospitalization



The CTC partnered with HSIAR, the BCCDC, and other epidemiology research groups to characterize the risk of hospitalization from Omicron in BC. Approximately 600,000 PCR test were included between January 3 to February 7, 2022, a period driven by the BA. 1 variant, where rapid antigen tests were not widely used, PCR testing centres were accessible, and therapy was not yet fully rolled out. Variables analysed that influenced risk that were included in the analysis were age, number of vaccine doses, and number and type of comorbidities (CEV 1, 2, 3 and non-CEV, as well as 1-2 vs. 3+ comorbidities). A chart review study was undertaken to exclude hospitalized patients who were incidentally diagnosed but did not require hospital-level care for severe or critical COVID-19, which comprised 60% of all cases. These thermal maps can continue to be used to guide clinical decision making and assessing risk vs. benefit of therapy.

Thermal Map of Hospitalization Risk from Omicron, excluding incidental diagnoses (Jan-Feb)

Please note that not all cells in the thermal maps are concordant with recommendations; general trends and other data were used



Thermal Map of Risk of Hospitalization and Recommendations for non-CEV Patients

The CTC would like to credit Kate Smolina and Christopher Mills and their team from the BCCDC and Heather Richards and her team from the HSAIR at the Ministry of Health for data and models provided in this guidance.

There are various limitations of this study, including inability to capture patients who did not pursue testing or asymptomatic patients, and excluding those few who received therapies such as sotrovimab. Despite this, this study represents one of the best-available risk models in Canada and is used by other jurisdictions such as Ontario, and groups such as CADTH.

Ongoing Validity of Risk Models

As BC risk models and thermal maps were developed during the first wave of Omicron (BA. 1), questions have emerged regarding the ongoing validity of this analysis in the BA. 2, BA. 5 and XBB waves of Omicron. There is a notion that most BC residents have had COVID-19, yet hospitalizations have remained low, hence the risk is overestimated in the thermal maps. Unfortunately, the analysis cannot be redone due to an inability to identify test-positive patients who self-test via rapid antigen tests.

Recent BC-specific evidence has suggested that the risk presented in **the thermal maps is over-estimated by approximately 2-3-fold.** A published BC analysis of nirmatrelvir/ritonavir during the Omicron waves showed that untreated patients in the CEV 1, 2 and 3 categories had a risk of hospitalization and mortality of 3.2%, 3.1% and 3.5%, respectively. Only CEV 2 individuals over 70 years had a risk exceeding 5%.

Furthermore, many BC residents have now been exposed to COVID-19 and have additional protection from natural infection. A recent BC study showed that even adults 80 years and older without hybrid immunity had a hospitalization rate of about 3.5%, whereas the current thermal maps estimated that risk to be

approximately double. The thermal maps continue to provide useful information about which factors influence the risk of hospitalization and mortality, but should no longer be used to actually calculate absolute risk for purposes of clinical decision making.

Summary of Trials

Nirmatrelvir/ritonavir

Nirmatrelvir is a protease inhibitor with a 2-hour half-life; it is co-administered with ritonavir to allow BID dosing. The landmark trial of nirmatrelvir/ritonavir has been published in the NEJM in February 2022.

EPIC-HR was a randomized double-blind placebo-controlled trial:

- 2246 adult outpatients with mild-moderate COVID-19 who were enrolled
- Patients had to be within 5 days or less of symptom onset
- Patients included had to be unvaccinated and at increased risk of developing severe disease, defined as age 60 or older or having a chronic condition such as diabetes, heart condition or chronic kidney disease
- The mean age of patients in the trial was 47; most had a single co-morbidity, the most common of which was smoking
- Patients were randomized in a 1:1 fashion to receive nirmatrelvir/ritonavir or placebo
- The primary endpoint was COVID-19-related hospitalization (not all-cause), or death from any cause.
- The primary endpoint occurred in 66/1064 (6.3%) patients given placebo vs. 8/1039 (0.8%) patients randomized to active treatment for a relative risk reduction of 88%, an absolute risk reduction of 5.5% and an NNT of 18.
- A high-risk subgroup of ~200 patients (those over 65 with more risk factors) was analyzed. This group, similar to the patients prioritized for treatment in this guide, experienced a nearly 15% absolute risk reduction in COVID-19 hospitalization (16.3% vs. 1%, $p<0.001$).
- Side effects that were drug-related included diarrhea, nausea, dysgeusia, muscle aches and hypertension. The rate of drug-related ADRs was 7.8% in the treatment arm vs. 3.8% in the placebo arm, for a NNH with one side effect of 25.

Based on these data, nirmatrelvir/ritonavir is given a AIIa recommendation by the NIH and a conditional recommendation by the IDSA to *suggest* treatment over no treatment.

Another RCT was also conducted by the manufacturer of nirmatrelvir/, but it remains unpublished, likely because it was negative.

Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR), unpublished

- This was a randomized, double-blind, placebo-controlled trial conducted by Pfizer.
- 1411 standard-risk individuals were randomized between August 2021 – February 2022 to receive nirmatrelvir/ritonavir or placebo within 5 days of symptom onset.
- Patients had to be at “standard risk” of hospitalization and death from COVID-19, meaning having a single risk factor such as age 65 or older, a single chronic condition, or lack of vaccination in younger individuals. Most patients were infected with the Delta variant of concern.
- There was no difference seen in the primary endpoint of time to sustained symptom alleviation, which was defined as the absence of key COVID-19 symptoms for 4 consecutive days.

- There was also no difference in hospitalization due to COVID-19 or all-cause mortality (0.9% vs.1.8%, p=0.187). The secondary endpoint of hospitalization and mortality was close to reaching statistical significance at the interim analysis, where the event rate in the placebo arm was 2.4%. However, due to the emergence of Omicron, the event rate in the placebo and treatment arms dropped to nearly zero, and recruitment stopped.

Real World Evidence

Various observational studies characterize the association of nirmatrelvir/ritonavir and hospitalization related to COVID-19. A detailed overview of studies that support these recommendations is presented here. While nirmatrelvir/ritonavir tends to be associated with a reduction in hospitalizations, the populations in these studies vary greatly depending on who is eligible to receive nirmatrelvir/ritonavir in that jurisdiction and to whom the drug is ultimately dispensed. Patients represented in observational studies are generally high-risk individuals with a hospitalization rate well above 3%. Various sub-group analyses show that while, on average, patients seem to benefit from treatment, the benefit is very strongly driven by high-risk individuals, who experience higher absolute risk reductions, with low-risk individuals seeing no reduction in their already low rates of hospitalization/mortality from COVID-19.

The literature consistently shows that hospitalization/mortality among treated individuals with risk factors does not generally drop below 1%. BC data also show that ~1% of patients experience serious adverse effects and that the ***safety concerns are likely to outweigh a potential benefit in patients with a risk of hospitalization from COVID-19 of less than 1%.*** Literature is also clear that risk factors such as age, vaccination status and comorbid conditions continue to be associated with a higher risk of hospitalization from COVID-19 and a greater likelihood of benefit. Lastly, subgroup analyses show that patients, except for those who are immunocompromised, need ***more than one risk factor*** to attain a risk of hospitalization of >1% and derive a benefit from nirmatrelvir/ritonavir. Groups of patients with a single risk factor, for example, age over 65 without under-immunization or chronic conditions, have been shown not to benefit from nirmatrelvir/ritonavir. A more detailed summary of studies used to support these recommendations are highlighted in Table 1. Studies that report outcomes in duplicate from the same data sets have been omitted. In short:

- *Arbel et. al. Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge, NEJM.*

  This was a retrospective, population-based cohort study from Israel conducted during the Omicron wave. Patients were eligible to receive nirmatrelvir/ritonavir if they scored 2 points or more on a scoring system – age over 65 was given 2 points, most chronic conditions were given 1 point and un-vaccination was given 9 points. 3,902 nirmatrelvir/ritonavir recipients were compared to 105,352 nirmatrelvir/ritonavir non-recipients for the primary endpoint of hospitalization and death in the 30 days of testing positive. The overall event rate in the study was very low (<1%). Those who had a higher risk of hospitalization/death (those 65 and older) saw a statistically significant benefit from nirmatrelvir/ritonavir (59 events / 100,000 patient days vs. 15 events / 100,000 patient days), whereas lower-risk individuals did not. Within those 65 and older, the benefit was driven by higher risk individuals such as those with immunosuppression (HR 2.23), cancer (HR 2.17), renal failure (HR 2.88), neurological disease (HR 2.01), COPD and diabetes (HR 1.5).

All other elderly with less severe comorbidities such as smoking, obesity and TIA did not derive a benefit from nirmatrelvir/ritonavir.

- *Yip et. al. Impact of the Use of Oral Antiviral Agents on the Risk of Hospitalization in Community Coronavirus Disease 2019 Patients (COVID-19), Clinical Infectious Diseases*

  This was a study of approximately 15,000 patients from China during the BA. 2 wave of Omicron. Those who received nirmatrelvir/ritonavir were compared to those who received standard of care for the primary endpoint of hospital admission 30 days after testing positive. Patients in the study had a median age of ~75 years old, 58% did not receive a primary vaccine series and most had multiple comorbidities, with 1/3 having a diagnosis of diabetes. Incidence of hospitalization was lower in nirmatrelvir/ritonavir users than in those receiving standard of care (3.5% vs. 1.6%). The high event rate was attributed to a large number of risk factors in the study population who were offered treatment.

- *Shah et al. Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 — United States, April–September 2022. MMWR*

  In the largest cohort study (750,000 individuals) from the US, nirmatrelvir/ritonavir recipients were compared to those who did not receive nirmatrelvir/ritonavir. Overall, there was a statistically significant reduction in hospitalization due to COVID-19 (0.47% vs. 0.86%); however, there were many subgroups that did not benefit from treatment, including those with 3 or more mRNA vaccine doses and those with 1 or no underlying health care conditions. Elderly patients were more likely to benefit, but those with no underlying health conditions saw no benefit from treatment, and their hospitalization rate was below 0.5% in both groups.

- *Schwartz et. al. Population-based evaluation of the effectiveness of nirmatrelvir–ritonavir for reducing hospital admissions and mortality from COVID-19. CMAJ*

  This was a population-based evaluation of the nirmatrelvir/ritonavir program in Ontario, Canada. Patients were eligible to receive nirmatrelvir/ritonavir if they were deemed high risk by the Ontario Science Table, which used the same eligibility criteria as British Columbia. Fully vaccinated patients were eligible only if they were over 70 years old and had 3 or more chronic conditions. The study showed a modest reduction in hospitalization and death from COVID-19 in nirmatrelvir/ritonavir recipients (2.1% vs. 3.7%). Those over 70 who were eligible had the highest risk of hospitalization and death and the highest risk reduction (2.8% vs. 5.0%). Of note, 1/3 of the population in this study were patients from LTC facilities (~30,000), who unfortunately did not benefit from nirmatrelvir/ritonavir (4.7% vs. 5.6%, OR 0.84 CI 0.66-1.06) in a statistically significant way. This study is often cited as showing that elderly benefit from nirmatrelvir/ritonavir; however, it is important to note that the elderly in this study had a very large number of comorbidities.

- *Kabore et al. Real-world effectiveness of nirmatrelvir/ritonavir on COVID-19-assocaited hospitalization prevention: A population-based cohort study in the province of Quebec, Canada. MedRXIV*

  In this cohort study, patients were eligible for nirmatrelvir/ritonavir in QC if they did not receive a primary series of COVID-19 vaccinations or were immunocompromised. Those over 70 could receive nirmatrelvir/ritonavir if fully vaccinated in rare cases at the prescriber's discretion. Overall, there was a benefit from nirmatrelvir/ritonavir (3.56% vs. 11.5%) in the primary endpoint of COVID-associated hospitalization; however, those fully vaccinated did not benefit (7.53% vs. 8.43% p=0.321) from treatment.

Most elderly in this study (76%) did not receive a primary vaccine series and those who received a vaccine dose in the last 6 months derived no benefit from nirmatrelvir/ritonavir (11.6% vs. 13%). The high rate of event was attributed to the fact that most patients in the study were unvaccinated.

- *Therapeutics Initiative: Paxlovid in British Columbia – an interim real-world analysis.* TI Letter

  This study was conducted in collaboration with the Therapeutics Initiative where groups of nirmatrelvir/ritonavir recipients (CEV 1, CEV 2, CEV 3 and non-CEV patients) and compared to non-recipients for the primary endpoint of all-cause hospitalization and mortality. Statistically significant differences were seen in the CEV 1 and CEV 3 populations, for a risk reduction of approximately 50%; CEV 2 patients experienced a reduction but did not reach statistical significance. Importantly, non-CEV experienced a higher, albeit non-statistically significant event rate after taking nirmatrelvir/ritonavir than non-recipients (1.9% vs. 1%). Non-CEV patients who were offered nirmatrelvir/ritonavir generally had multiple risk factors such as age, lack of optimal vaccination and 3 or more comorbidities.

Nirmatrelvir/ritonavir for symptom relief or to prevent Long COVID

Other potential benefits of nirmatrelvir/ritonavir have thus far not been consistently shown in the literature. As demonstrated by EPIC-SR, nirmatrelvir/ritonavir has no impact on the time to symptom alleviation. Another study of a novel compound VV116 vs. nirmatrelvir/ritonavir in symptom resolution showed that on average, patients had 5.5. days of symptoms irrespective of the drug they took, virtually identical to an observational cohort of patients from the same region in the same time period. The impact of nirmatrelvir/ritonavir on post-COVID condition, or long COVID, is also inconsistent. For example, a recent study from California showed that nirmatrelvir/ritonavir takers experienced a slightly higher, non-statistically significant rate of post-COVID condition based on self-reports, whereas a study published by the Lancet claimed to observe a benefit in treated patients when ICD-10 codes for non-specific conditions such as diabetes, arrhythmia and shortness of breath were taken to represent development of post-COVID condition.

Remdesivir

Remdesivir is an intravenous antiviral initially evaluated in severely ill inpatients with COVID-19 requiring oxygen support in a landmark trial ACTT-1. Health Canada approved it for this indication, and some nationally procured supply remains unused due to subsequent data showing its lack of impact on meaningful outcomes in the severely ill population.

In December 2021, a trial called PINETREE was published:

- The 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 the 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, 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, and no patients died by day 28.
- Remdesivir was generally well tolerated; transaminases may need to be monitored in patients with baseline elevations of liver enzymes. Remdesivir has been given to patients with renal disease with and without dose adjustments; however, it was not evaluated in this trial, and this population was excluded from Canadian labelling.

Remdesivir has the advantage of having few drug interactions while maintaining comparable risk reductions to nirmatrelvir/ritonavir. However, the 3-day IV dosing regimen is difficult to administer, and the CTC recommends that it be used if nirmatrelvir/ritonavir cannot be prescribed only in the highest-risk population (patients with a ≥ 5% risk of hospitalization from Omicron). The NIH recommends remdesivir as an alternative to nirmatrelvir/ritonavir with a Grade BII rating. The IDSA suggests remdesivir with a conditional rating and low certainty evidence.

Sotrovimab:

Sotrovimab has been evaluated in a single peer-reviewed, double blind, randomized-placebo controlled trial (COMET-ICE):

- 1057 patients with mild symptoms of COVID-19 and at least one risk factor for disease progression were included
- Patients were randomized to receive a single dose of sotrovimab 500mg IV compared to placeb
- Most patients were younger (<50) and had one single chronic condition, with obesity being the most prevalent comorbidity
- The primary endpoint was a composite outcome of all-cause hospitalization for >24 hours or death within 29 days of the receipt of the infusion
- Out of the 528 patients who received sotrovimab, 6 met the primary endpoint of hospitalization or death vs. 30 of the 529 who received placebo (1% vs. 6%; p<0.001; ARR=5%, NNT=20). There were only 2 deaths observed (placebo arm); the primary endpoint was driven entirely by hospitalizations.
- Hospitalizations were consistent with progressive COVID-19 requiting oxygen support and hospital-level care; only 1 hospitalization was not COVID-related
- Secondary outcome results demonstrated that sotrovimab significantly reduced progression to severe/critical respiratory COVID-19 compared with placebo (1 vs. 5% p=0.002)
- Sotrovimab did not reduce length of stay or ICU-bed-days
- The proportion of patients reporting adverse events was similar between treatment groups; sotrovimab was well tolerated, and no safety concerns were identified; 6 patients in each placebo and sotrovimab groups experienced mild to moderate infusion reactions.

The COMET-ICE trial was well conducted, with a high degree of generalizability posing no major concerns during critical appraisal. Sotrovimab is given a positive conditional recommendation by the Infectious Diseases Society of America and a Grade AIIa recommendation supporting its use by the NIH.

Tixagevimab/cilgavimab

Tixagevimab/cilgavimab is a long-acting monoclonal antibody cocktail initially approved in Canada for the prevention of COVID-19 in those who are unlikely to mount an adequate immune response to COVID-19 vaccination or in whom such vaccination is contraindicated.

Tixagevimab/cilgavimab was also evaluated for treatment in a double-blind placebo-controlled trial called TACKLE:

- 910 unvaccinated patients with mild-moderate COVID-19 presenting within 7 days of symptom onset were assigned in a 1:1 fashion to receive tixagevimab/cilgavimab 600mg IM x 1 dose or placebo
- The primary endpoint was COVID-19 hospitalization or death from any cause through day 29
- The median age of participants was 46.1 years; 90% were at high risk of progression of COVID-19 defined as age over 65 or presence of a comorbidity. The most commonly occurring comorbidities were obesity, smoking and hypertension.
- Out of the 415 patients who received placebo, 37 (9%) met the primary outcome vs. 18/407 (4%) in the tixagevimab/cilgavimab arm for an adjusted relative risk reduction of 50.5% [95% CI 14.6–71.3]; p=0.0096
- The absolute risk reduction was 4.5% (95% CI 1.1–8.0; p<0·0001), for a number needed to treat of 22
- Tixagevimab/cilgavimab was generally well tolerated, and no differences between it and placebo were observed (29% vs. 36%)
- There was one myocardial infraction and one sudden cardiac death, both in the tixagevimab/cilgavimab arm

Overall, the TACKLE trial, which was carried out mainly during the delta wave and was similar to trials of nirmatrelvir/ritonavir, remdesivir and sotrovimab, demonstrated a lower relative risk reduction than those agents, despite the baseline hospitalization rate being slightly higher.

Molnupiravir

Molnupiravir is a nucleotide analogue which when incorporated into viral RNA causes base-pair mismatch leading to mutations and viral catastrophe. Regulators have scrutinized the drug's mechanism of action for the theoretical fear of promoting the emergence of variants of concern due to promoting mutations and reproductive safety.

Molnupiravir was evaluated by a randomized, double-blind placebo-controlled trial called MOVe-Out:

- 1408 outpatients with mild-moderate COVID-19 presenting within 5 days of symptom onset were assigned in a 1:1 fashion to receive molnupiravir 800mg PO BID x 5 days or placebo
- The primary endpoint was all-cause hospitalization or mortality within 29 days
- The trial stopped when a pre-planned interim analysis revealed that it met the primary endpoint with a 50% relative risk reduction and a p-value (set at p<0.0092 to allow for alpha spending), which was statistically significant.
- In that analysis, 28/385 (7.3%) of patients on active treatment experienced the primary outcome, vs. 53/377 (14.1%) who received a placebo, for an ARR of 6.8%. Trial recruitment stopped, but there were still another ~600 patients who were undergoing 29-day follow-up.
- The final analysis, published in December 2021, discovered that the ARR for the entire trial population declined to just 3%, with 6.8% (48/709) patients in the treatment arm experiencing the primary outcome vs. 9.7% (68/699) in the placebo arm.

- This difference, if the same pre-specified p-value from the interim analysis is applied, is not statistically significant (p=0.0218. A time-to-event analysis depicted by a Kaplan-Meier curve is also not statistically significant.
- Data from the FDA reveal that during the second half of the study, the event rate was numerically higher in the molnupiravir arm than in the placebo arm (20 vs. 15 events, respectively).
- The primary outcome was driven by very high event rates (>20%) that were apparent in countries like Brazil. In contrast, higher-income countries like the US had no appreciable reductions in hospitalization resulting from the effects of the drug.

Molnupiravir carries the advantage of having few or no drug-drug interactions and is not impacted by renal or liver disease. Such details, however, are not currently available as the drug is undergoing evaluation by Health Canada, and the monograph has not been issued in Canada.

Repurposed Therapies

The CTC has evaluated various other therapies that are not routinely recommended, including colchicine and the above-mentioned SSRI fluvoxamine.

In short, Colchicine was evaluated at 0.6 mg PO BID x 3 days, then 0.6 mg daily x 27 days in a single large Canadian RCT (COLCORONA) and demonstrated a reduction in progression of COVID-19 and hospitalization in a sub-group of patients with PCR confirmed COVID-19. The trial was stopped early; due to decreased power leading to the low certainty of its results and a higher risk of adverse events (diarrhea and blood clots). Guidelines (WHO, NIH) do not recommend colchicine. The CTC states that if colchicine is used outside of clinical trials, full disclosure of risks and benefits with consideration of patient values is necessary. Overall, the drug uptake in BC has been very low to none.

Fluvoxamine was evaluated at 100 mg PO BID x 14 days in a Brazilian RCT and shown to reduce emergency room visits > 6 hours, a surrogate endpoint for hospitalizations. It has not demonstrated a benefit in reducing actual hospitalizations from COVID-19, length of stay or mortality. For every 12 trial participants, one additional patient stopped fluvoxamine prematurely. Due to low generalizability from a very high event rate and lack of robust safety data, guidelines (e.g., IDSA) do not recommend using fluvoxamine outside clinical trials. A Canadian fluvoxamine study stopped enrolment due to futility. The CTC states that if fluvoxamine is used outside of clinical trials, full disclosure of risks and benefits with consideration of patient values are necessary. Additional concerns were also posed about the lack of full safety evaluation with this dose. The recommended starting dose in patients over 55 is 25mg daily, whereas the trial's dosing was 8 times that dose. As fluvoxamine can cause various side effects such as hypotension, dizziness, falls, QT prolongation and GI effects, the safety of this regimen deserves further study before the drug can be routinely used for treating COVID-19.

Five trials have evaluated inhaled steroids for the symptomatic relief of COVID-19 manifestations such as shortness of breath and cough, showing that treatment with inhaled steroids reduces symptoms and may reduce the need for hospitalization (although the latter has not been consistently demonstrated and has thus far been a secondary endpoint of most trials). Due to familiarity and safety, inhaled budesonide 800 µg twice daily or ciclesonide 320 µg twice for 14 days may be considered on a case-by-case basis in adults with

lower respiratory tract symptoms of COVID-19 aged 65 and over or aged 50 and over with underlying health conditions and within 14 days of symptom onset, acknowledging the limitations of these trials. There is no evidence to combine inhaled steroids with nirmatrelvir/ritonavir or remdesivir; some inhaled steroids interact with nirmatrelvir/ritonavir.

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