BC COVID THERAPEUTICS COMMITTEE (CTC)

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

November Update: NEW
- Recommendation language for monoclonal antibodies, including tixagevimab/cilgavimab
- Guidance in the context of resistant Variants of Concern
- Impacts of waning, second boosters, hybrid immunity and bivalent vaccines
- Recommendation in those with reduced or unknown renal function
- Recommendations regarding rebounds, re-infections, and retreatments and
- Discussion regarding validity of currently used risk scoring models.

October Update: NEW Test-to-Treat Guidelines have been released. Read how patients with COVID-19 should be tested to ensure optimal treatment access. See Testing

GENERAL INFORMATION

Agents available for treatment of COVID-19

Various agents are available in BC for the treatment of COVID-19 in mildly-moderately ill patients. These therapies include a monoclonal a direct-acting oral antiviral **nirmatrelvir/ritonavir** (Paxlovid) and an IV antiviral, **remdesivir** (Veklury). A monoclonal antibody (mAB) **sotrovimab** (Xevudy) has also been shown efficacious in treating mild-moderate illness; however, it has reduced activity against many variants currently circulating in BC. A monoclonal antibody cocktail **tixagevimab/cilgavimab** (Evusheld) has recently been approved by Health Canada for treatment, in addition to its prophylaxis indication. Finally, another oral antiviral, **molnupiravir** (Lagevrio) is currently being considered for Health Canada approval. Guidance on previously available repurposed therapies is also included (**inhaled steroids, fluvoxamine, colchicine**). This document provides general recommendations for the use of these therapeutics and supporting evidence, with additional practice tools available separately. *See Toolkit #1 – Step-by-step Assessment for practical prescribing information.*

RECOMMENDATIONS

Complete eligibility for nirmatrelvir/ritonavir (Paxlovid) includes:

- 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 vaccine status** or previous infection. *(See also Practice Tool 2 – CEV Definitions).*

- **Unvaccinated individuals** without previous infection **who are EITHER:**
  - **≥50 years OR**
  - have **three or more chronic conditions/co-morbidities***

- **Individuals ≥ 50 years with 1-2 vaccine doses** or previous infection alone, **with three or more chronic conditions/co-morbidities***

- **Individuals aged ≥70 years with 1-2 vaccine doses** or previous infection alone, **with one or more chronic condition/co-morbidity***

- **Individuals ≥ 70 years with three or more chronic conditions/co-morbidities***, **regardless of vaccine status** or previous infection

- **Indigenous individuals** (if not captured above) **who are EITHER:**
  - **unvaccinated** without previous infection OR
  - **≥ 50 years with 1-2 vaccine doses** or with previous infection alone OR
  - **≥ 70 years regardless of vaccine status** or previous infection

*Chronic conditions include ANY medical conditions requiring follow-up, monitoring or chronic medications, e.g., obesity, smoking, diabetes, heart failure, heart disease, stroke, neurological conditions, and are determined at the discretion of the prescriber.
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

Therapy Recommendations

Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days (150/100mg PO BID x 5 days in eGFR 30-60ml/min) **is recommended** within 5 days* of symptom onset to patients with a **5% or greater risk^** for hospitalization or progression to severe COVID-19

OR, if nirmatrelvir/ritonavir cannot be given to patients with a 5% or greater risk 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 <30ml/min) **is recommended** within 7 days of symptom onset as an alternative to nirmatrelvir/ritonavir

Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days (150/100mg PO BID x 5 days in eGFR 30-60ml/min) **is suggested** within 5 days of symptom onset to patients with a **3-4% risk^** of hospitalization or progression to severe COVID-19. As treatment effect is not directly known in this population, the estimated benefit needs to be weighed against potential risk of adverse effects in consideration with patient's values and preferences

Due to a limited drug supply, operational constraints and unclear benefit in lower risk individual, patients with a risk of 5% or greater are currently being prioritized and offered treatment with remdesivir.

^To quantify the risk based on patient factors, see Risk Assessment and Local Data below
*The symptom window can be extended to 7 days in patients with a 5% or greater risk if they would otherwise be referred for remdesivir solely based on its longer treatment window

THERE IS NO INDICATION TO COMBINE THESE THERAPIES: Due to drug scarcity and limited additional benefit, patients should receive ONE COVID-19-specfic therapy.

Sotrovimab 500mg IV X 1 dose has reduced efficacy against the BA. 5.1, BA. 5.2 and 5.2.1 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 BA. 5 VoCs. Sotrovimab has unknown clinical efficacy against many currently circulating VoCs (e.g., BA. 4.6, BQ. 1, BQ 1.1, XBB and BF. 7) 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 to 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 budesonide 800 µg twice daily for 14 days may be considered on a case-by-case basis in patients who have lower respiratory tract symptoms (cough, shortness of breath) for symptom relief. There is no evidence of additional benefit of inhaled steroids to antivirals or antibody therapy

Tixagevimab/cilgavimab 600mg IM x 1 dose 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. If tixagevimab/cilgavimab is used as a last line treatment in cases where nirmatrelvir/ritonavir, IV remdesivir or sotrovimab cannot be used, disclosure to patients of risks, including cardiovascular serious adverse events (SAEs), and benefits and consideration of individual circumstances (clinical and immune status, patient values, logistics) is necessary. The convenience of the IM route of administration of tixagevimab/cilgavimab should not be the primary indication for use.

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 and potential risk of adverse events and additional immunosuppression in this population.

Fluvoxamine is not recommended due to low certainly 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 who have a wide range of risk and are imprecise. Priority criteria for this guide were developed utilizing provincial multi-variable modelling to identify patients who would benefit most from treatment using age, vaccine status and type and number of co-existing chronic conditions/co-morbidities.

Patients who are likely to have a clinically meaningful reduction in hospitalization are those who have a risk of hospitalization of at least 3% from Omicron. Such patients were selected to be eligible for therapy; however, **patients who are most likely to benefit based on evidence from clinical trials are those with a risk of ≥ 5%. Such patients are eligible to receive nirmatrelvir/ritonavir, and if contraindications or drug-drug interactions prohibit administration, remdesivir as an alternative.** Those who have a slightly elevated risk from average (3-4%) are eligible for nirmatrelvir/ritonavir, but the paucity of data that informs the magnitude of benefit and the balance between risk vs. potential benefit needs to be acknowledged and incorporated into the decision to treat. Currently, patients with a risk of ≥5% are prioritized for remdesivir.

Risk can be estimated using a scoring system below. The scoring system accurately predicts the risk category from the BC-specific analysis 98% of the time and is 100% concordant with the CTC overall eligibility criteria.

Within these point categories, however, the absolute risk still varies. Even within the highest-risk priority group, a wide range of risk exists; risk increases by age number of comorbidities and incomplete vaccination status. Each additional chronic condition/co-morbidity also increases risk. This document provides guidance only; **patients defined above or those who score 4 or more points are those who *may benefit* from treatment – case-by-case assessment is still required, and the totality of risk factors needs to be considered when offering treatment.** This risk is conservative and likely overestimated.

Point Scoring to Estimate Hospitalization Risk	
Age (select ONE)	**Point Value**
70+	2
50-69	1
<50	0
Vaccine Status (select ONE)	
Unvaccinated AND no previous infection	3
Vaccinated with 1 or 2 doses OR previous infection alone	1
Vaccinated with booster (3 doses) OR previous infection + any vaccination	0
At-Risk Conditions (select ONE with the highest value)	
CEV 1 (Severe Immunocompromise)	6
CEV 2 or CEV 3	4
Indigenous	2
3+ chronic conditions/comorbidities	2
1-2 chronic conditions/comorbidities	1
no chronic conditions	0
Add the points from the three sections	

Legend: Estimated Hospitalization Risk

3 points or less: No increased risk; treatment is not recommended
4 points: Slightly increased risk (3-4%); treatment is suggested
5 points: Increased risk (5-9%); treatment is recommended
6 points or more: Highest risk (≥ 10%); treatment is recommended

*Chronic conditions include e.g., obesity, smoking, diabetes, heart failure, heart disease, stroke
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, treatment for solid tumors, advanced 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/chronic ventilation, cancer not captured above

Local Data and Risk Models

Therapies recommended in this guide were evaluated in the pre-Omicron wave; variants of concern (VoCs) in trials included predominantly Delta, with other VoCs comprising a small fraction of sequenced virus. Nirmatrelvir/ritonavir, remdesivir and sotrovimab were shown to reduce the risk of disease progression (i.e., hospitalization or development of severe COVID-19) from about 6% to about 1%, for a relative risk reduction of ~85%, an absolute risk reduction of 5% and a number-needed-to-treat of ~20.
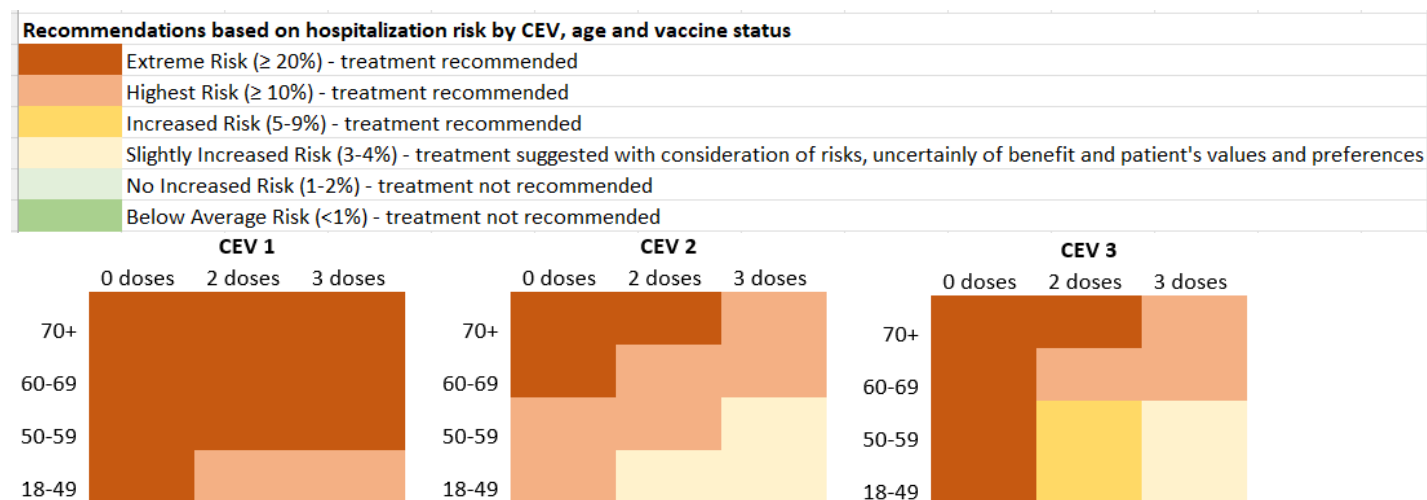
During the Omicron wave, the risk of hospitalization in BC has decreased drastically to 1.2% from 6.3% in the preceding period. As such, patients who are offered treatment need to be carefully selected for therapy to yield clinically meaningful reductions in hospitalizations.
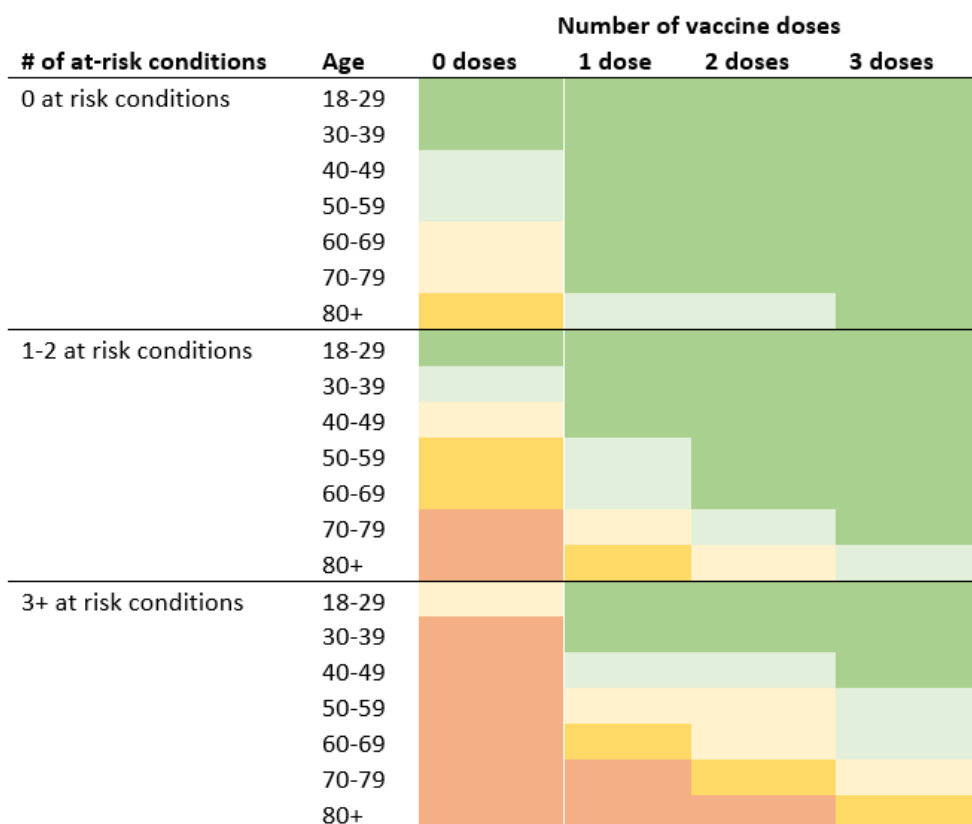
BC Study of Risk of Hospitalization

The CTC has 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 that were found to influence 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). An additional chart review study was undertaken to exclude patients who were hospitalized after testing positive but were incidentally diagnosed and did not require hospital-level care for severe or critical COVID-19, which comprised 60% of all cases.

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

Recommendations based on hospitalization risk by CEV, age and vaccine status

- Extreme Risk (≥ 20%) - treatment recommended
- Highest Risk (≥ 10%) - treatment recommended
- Increased Risk (5-9%) - treatment recommended
- Slightly Increased Risk (3-4%) - treatment suggested with consideration of risks, uncertainly of benefit and patient's values and preferences
- No Increased Risk (1-2%) - treatment not recommended
- Below Average Risk (<1%) - treatment not recommended

CEV 1 / CEV 2 / CEV 3 thermal maps by age (70+, 60-69, 50-59, 18-49) and doses (0 doses, 2 doses, 3 doses)

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

Number of vaccine doses

# of at-risk conditions	Age	0 doses	1 dose	2 doses	3 doses
0 at risk conditions	18-29				
	30-39				
	40-49				
	50-59				
	60-69				
	70-79				
	80+				
1-2 at risk conditions	18-29				
	30-39				
	40-49				
	50-59				
	60-69				
	70-79				
	80+				
3+ at risk conditions	18-29				
	30-39				
	40-49				
	50-59				
	60-69				
	70-79				
	80+				

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 and BA. 5 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. However, while the analysis cannot be redone due to an inability to identify test-positive patients who self-test via rapid antigen tests, various experts agree that this analysis remains a valid risk assessment useful for therapy eligibility for the following reasons:

- Wastewater surveillance data has indicated that there has been no other 5-week period, including during the April and June waves, where the number of people infected with COVID-19 had been substantially higher (and would thus greatly increase the denominator), than in the January-February study period. As hospitalizations after testing positive for SARS-COV-2 have remained stable over the last 9 months and through the April and June waves, the risk of hospitalization is likely also stable and still reflected by these thermal maps.

- Infection rates with the Omicron variant, which would increase the denominator in these models, have also been relatively infrequent in populations that are eligible for treatment in BC, namely the CEV populations and the elderly. For example, data from the Canadian Blood Services show that while nearly 80% of younger BC residents have contracted COVID-19, that rate is only about 40% in those over the age of 65. Similar trends have been observed in the UK.
- Real world data from jurisdictions that record rapid antigen test results, such as Israel, have not indicated a change in hospitalization risk in untreated patients throughout the various Omicron waves. For example, a large retrospective study from Israel that used a point system to identify patients eligible for treatment showed that untreated patients who have an ~2% risk of hospitalization have a combination of risk factors that would lead to the same risk estimate using BC thermal maps.
- While hybrid immunity (from vaccination and infection) has been shown to reduce the rate of re-infection with Omicron, it has not shown to reduce the risk of hospitalization beyond the high vaccine effectiveness against hospitalization conferred by vaccination alone. As such, even if a high proportion of BC's population has hybrid immunity, there is no strong data to support an adjustment of their hospitalization risk in these thermal maps by any factor.

Variables in the Model
- CEV status: Patients categorized as CEV Group 1 have the highest risk of hospitalization, requiring ICU-level care and death; although the receipt of 3 or more doses (achieved in >80% of this population) mitigates this risk, they still experience hospitalizations rates of over 10% especially if elderly. Incidental COVID is also less likely in this population. Patients in CEV Group 2 and Group 3 have a lower risk of hospitalization than Group 1, and patients who are less than 50 and have received a booster have only a very slight increase in risk. Combined, CEV groups 1 and 2 have 2.5-4 times the likelihood of hospitalization than the general population of the same vaccine status and age category.
- Vaccination Status: Vaccination greatly reduces the risk of hospitalization from infection with the Omicron variant. Vaccination with 2 doses reduces the probability of hospitalization by a factor of 3; a third dose is associated with a 6.4-fold reduction of hospitalization. A fourth dose (second booster) addresses waning of immunity in those who are less likely to mount a strong immune response; although long-term data is lacking, waning protection against hospitalization has been seen after 4-6 months. In the lower-risk general population, a 3rd or 4th vaccine doses do not lead to a large absolute change in the risk of hospitalization, whereas in higher-risk groups, this change is significant enough that a 2-dose series is considered sub-optimal, especially since patients who have not received a booster have likely received second doses more than 6 months ago.
- Age: Age is a well-known 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, still significant hospitalization rates despite the decreased likelihood in the Omicron wave, whereas individuals younger than 50 have a hospitalization rate of <1 - 2.5%, even if unimmunized. Age is also a confounding factor for chronic conditions/co-morbidities, which further increase the risk of hospitalization.
- Number of chronic conditions/co-morbidities: Completely healthy individuals, even if unvaccinated, have a low risk of hospitalization except perhaps for those with very advanced age. The number of chronic conditions, as

opposed to the type of co-morbidity, is a strong predictor of hospitalization across all age groups. Those with three or more chronic conditions need to be specifically considered as even 2 or 3 vaccine doses does not fully mitigate the risk of multi-morbid elderly patients. Most common co-morbidities increase the odds of hospitalization 2 to 3-fold; the type of co-morbidity does not seem to matter a great deal if not included in the CEV criteria. For example, those with substance use disorder have a similar increase in risk to those with non-insulin requiring diabetes.

Impact of Waning

Vaccine effectiveness (VE) against severe disease requires a definition of hospitalization that can discern incidental COVID-19 diagnoses vs. hospitalizations for COVID-19 as the cause. The UK surveillance report, which has implemented stricter criteria to accurately define COVID-19 hospitalizations, showed that in older adults, the vaccine effectiveness of a booster peaked at weeks 5-9 to 89%, and fell to approximately 75.4% 40 weeks or more after administration, with confidence intervals overlapping. Consensus estimates of vaccine effectiveness of the Pfizer and Moderna vaccine against the BA. 5 variant of concern is estimated to be about 60% at 9 months or more, compared to 85% at 4-6 months after a booster dose compared to unvaccinated people. **Despite these declines, the absolute risk of hospitalization would not expand the eligibility criteria for treatment for most patients in BC.** For example, those with a 2% risk of hospitalization according to the thermal maps may experience a 25% relative risk increase to 2.5% but remain ineligible for treatment. As these thermal maps have rounded up the risk of hospitalization and thus eligibility criteria to the nearest whole percent, those who are on the cusp of meeting treatment criteria (2.5% and greater) have already been included as eligible for treatment as their risk has been rounded up to 3%.

Second Boosters

Vaccine effectiveness against hospitalisation for fourth doses (second boosters), estimated using those 25 to 39 weeks post their third dose as the baseline group, was evaluated using a UK study compared in older adults aged 75 and over. VE was significantly higher in those who received a second booster at weeks 2-14, peaking at weeks 2-4, with an additional 58% increase in effectiveness against severe disease. However, at 15 weeks, the additional protection waned towards baseline, and at 4 months it was no longer higher than in those who received 3 doses. Studies of immunocompromised patients show similar VE results.

Due to a relatively short period of additional protection, boosted patients are generally considered in the same risk category irrespective of the number of boosters they received when being assessed for treatment eligibility. **However, prescribers assessing patients who have received a second booster dose in the last 4 months should acknowledge that the risk of hospitalization is likely 30-50% lower than calculated in the BC risk models. Treatment may be therefore withheld in such patients in the 3-4% risk category, should they become infected with COVID-19 within 2-19 weeks of their second booster, as their risk of severe disease is likely below 2%.**

Hybrid Immunity

Various studies have shown that hybrid immunity, i.e., immunity achieved through vaccination and infection, confers greater protection against subsequent infection, particularly from the Omicron variant where vaccine effectiveness against symptomatic infection is low. However, protection from severe disease has not been shown to improve over vaccination alone, particularly in those who received a booster. For example, one study showed that rates of hospitalizations were 0.5 per 100,000 patient days in those with hybrid immunity vs. 0.4 per 100,000 patient days in the three-dose cohort. The point system used to assess treatment eligibility considers the partial protection that previous infection confers, and hybrid immunity is treated as a boosted vaccine series in the risk assessment. However, as many patients in BC have received three vaccine doses and also have hybrid immunity, **no additional risk adjustment is applied to further lower the risk score of those who have received three vaccine doses.**

Bivalent Vaccine

The bivalent vaccines used in BC include the Moderna (Spikevax) vaccine, which targets the original SARS-CoV-2 virus from 2019 and the Omicron (BA.1) variant, and the Pfizer (Comirnaty) vaccine which exists as the original strain plus the BA.1 variant, as well as the original strain plus the BA.4/5 variant. While trials of all three vaccines have been conducted, all trials used serological endpoints only. There is currently no data to characterize these vaccines' effectiveness against severe disease in comparison to vaccines which target the original strain only. **As such, all mRNA vaccines are considered equivalent in the risk assessment and eligibility for treatment in BC at this point.**

Testing

Any recent positive test result in patients who are eligible for treatment is acceptable as a part of making the diagnosis of COVID-19. **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.**

New testing guidelines issued by the BCCDC in collaboration with the CTC focus on testing using Rapid Antigen Tests. A recent evaluation of patients who accessed outpatient therapeutics in BC showed that 83% 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. RATs are also cost-effective over more expensive testing methods. 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.

Patients should be encouraged to get tested if they are symptomatic. If the test is negative and the patient continues to feel sick or have worsening symptoms, they should be directed to repeat the test in 24 hours. **As long as they are within 5 days of symptoms starting, and not improving, 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 who are concerned about their symptoms should contact their health care provider for guidance. 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.

Testing information can be found at http://www.bccdc.ca/Health-Professionals-Site/Documents/BCCDC_PHL_Updated_nCoV_Lab_Guidance.pdf

Evidence:

Studies show that RATs offer excellent specificity, but lower laboratory sensitivity over PCR methods. For example, a Cochrane review cited that while specificity of RATs in individuals was over 99%, on average, the sensitivity was found to be 82% if patients tested within the first week of symptoms. 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 to recommend serial RAT testing for all symptomatic individuals as the optimal testing strategy to ensure maximum sensitivity. Health Canada's Medical Device Directorate will align with the US FDA's approach, and the evolving science, to maximize COVID self-test performance for detecting symptomatic with these new serial screening protocols. 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, as opposed to a longer interval between tests.

Testing and Treatment Evidence

There are currently no studies that 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 initiate 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 in fact 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 PCR Test

PCR 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. PCR 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. PCR is also used when there is a need to diagnose influenza (these tests are done together).

For patients who live in a 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 more comprehensive clinical investigation might be appropriate due to barriers in 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.

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

- High-risk patients (≥ 5% risk of progression to severe disease) who test negative despite serial RATs
- Patients with a very high-level of suspicion (e.g., symptomatic with a household contact) who test negative despite serial RATs
- Patients in whom therapy was initiated despite a negative RAT(s) to ensure a diagnosis of COVID-19
- 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 PCR tests available vary (e.g., saline gargle tests, NP swabs) and are subject to change. Health care providers wishing to order PCR testing should consult their local Health Authority resources for up-to-date guidance. As PCR testing results may take 24 hours or more, **patients for whom treatment is indicated should also perform serial RATs while awaiting PCR results.**

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. Furthermore, VoCs circulating in BC fluctuates greatly from week to week, offering limited visibility

As of November 5th, 2022, the following proportion of VoCs have been isolated in BC. The table also depicts the decrease in binding to tixagevimab/cilgavimab and sotrovimab.

Variant of Concern	% of total VoCs (n=219) Oct 30 to Nov 5, 2022	Fold reduced neutralizing susceptibility	
		Tixagevimab/cilgavimab	Sotrovimab
BQ. 1	19.6%	476	23
BQ. 1.1	6.4%	476	75
BA. 2.75.2	2.7%	322	7.9
BF. 7	9.6%	> 1000	49
BA. 4.6	1%	322	41
Other BA.5	60.7%	25	23

Sotrovimab: Reasonable susceptibility and clinical efficacy is expected for sotrovimab at a 23-fold reduction in binding on the basis of 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. The hospitalization rate in this RCT of this high-risk population was 0.95% vs. 2% when compared to an active control (molnupiravir). At this cut-off, approximately 16.5% of VoCs in BC are likely resistant to sotrovimab.

Tixagevimab/cilgavimab: There is no real-world clinical data that 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 39.3 % of VoCs in BC are highly resistant to tixagevimab/cilgavimab.

Symptoms and Symptom Progression

Patients offered treatment should be **appreciably symptomatic from COVID 19.** 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 have been shown to be associated with higher risk of illness progression. *Great deal of case-by-case clinical judgement 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.*

Illness trajectory is a useful in establishing 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 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** (and sotrovimab or tixagevimb/cilgavimab, if used in extenuating circumstances) **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 the ≥5% 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 an active treatment or placebo. Furthermore, most patients produced their own 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 who are hospitalized for other reasons and are mildly-moderately ill with COVID-19 can be considered for treatment if they meet the eligibility criteria. Many patients admitted to hospital are incidentally diagnosed or are part of nosocomial outbreaks and are offered testing with very low thresholds that often does not warrant treatment. As with all mild-moderately ill patients offered treatment, patients in hospital need to be appreciably symptomatic, have a valid COVID-19 test, be assessed for contraindications and drug-drug interactions, and offered treatment on the basis of their risk of progression to severe disease. Even though patients are already hospitalized, the goal of such therapy is still 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.

Contraindications

Nirmatrelvir/ritonavir should not be used in end-stage liver disease (Child-Pugh C). In patients with hepatitis B and C, or HIV infection regardless of treatment status may benefit from Specialist Consultation (e.g., Infectious Diseases, HIV Specialist), but 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 in place before prescribing. If drug-drug interactions pose safety concerns, treatment can be forgone, especially in those who have a very slightly increased risk of hospitalization (3-4%).**

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 currently conducting a small trial in patients with eGFRs less than 30ml/min and safety and efficacy data are forthcoming. At this time, according to nephrology experts in BC, 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 thought to be dangerous in such patients, and a lack of a 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 be used to guide treatment decisions. Boarder-line eGFR (e.g., 28ml/min) should be assessed using clinical judgement 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 any of 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 like sotrovimab and tixagevimab/cilgavimab can cause hypersensitivity reactions and infusion/injection reactions, although they are rare.

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, in those trying to conceive and in 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 who are on oral contraceptives should use a back-up method when taking nirmatrelvir/r due to drug interactions leading to lower plasma levels of estrogen, 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 has significant loss of 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 to be at lower risk of developing severe COVID-19 illness and requiring hospitalizations compared to adults with immune compromise. Risk of severe COVID disease in immunocompromised children appears to be related to underlying comorbidities rather than immune suppression itself. Immunocompromised children may present with atypical signs and symptoms of COVID-19 that can fluctuate rapidly between being asymptomatic to having mild to moderate symptoms and vice versa. Information on COVID-19 vaccine immunogenicity in children with immune compromise is currently limited.

In consultation with pediatric infectious diseases and appropriate subspecialist, treatment with 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 assessments 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 being pursued, infusions can be arranged at BC Children's hospital through the patient's BC Children's Main Responsible Physician/Service, as 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 the clinical relevance of this interaction 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.

Renal Dosing of nirmatrelvir/ritonavir

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. There is no dose adjustment 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. There are no dose adjustments 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)*. Patients in Long-Term Care are eligible for treatment if they meet criteria, with an understanding that IV therapeutics cannot be administered easily in LTC settings. Patients may also be offered treatment in Emergency Departments. 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 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 judgement. 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 who have 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 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 virus beyond detectable levels without complete clearance, and once the 5-day course is completed, the virus begins to replicate again, causing a rebound of illness. However, rebounds have since been shown to occur irrespective of whether treatment is given or not 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 previous infection confers. Studies show that re-infection rates in a highly vaccinated population are highest in the 18–29-year-olds (~15%) and about 10% in the general population.

Retreatment

The CDC does not recommend routine re-treatments of rebounds. Rebounds have been shown to be 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 who have significant symptoms or rapidly progressing illness. Another 5-day course should be used; there is no evidence that supports longer courses of treatment, although a 10-day course is currently being investigated by the manufacturer.

Re-infections should be assessed and treated as new infections. Patients' 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
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. Nirmatrelvir/r has been evaluated in a phase 3 clinical trial EPIC-HR, which was 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 was analysed (those over 65 with more risk factors). This group, which is 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.

Remdesivir

Remdesivir is an intravenous antiviral initially evaluated in severely ill inpatients with COVID-19 requiring oxygen support in a landmark trial ACTT-1. It was approved by Health Canada 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 widespread use of vaccination and the availability of proven treatments making randomization to placebo ethically challenging
- The primary outcome was COVID-19–related hospitalization or death from any cause
- 2 of 279 patients (0.7%) in the remdesivir group and in 15/283 (5.3%) in the placebo group met the primary endpoint, p=0.008.
- This equated to an 87% relative risk reduction, a 4.6% ARR and a NNT of 22, which is slightly higher than nirmatrelvir/ritonavir or sotrovimab (17 and 20, respectively).

- o A total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a COVID-19–related medically attended visit by day 28 an no patients died by day 28.
- o 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 is excluded from Canadian labelling.

Remdesivir has the advantage of having few drug interactions while maintain 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):
- o 1057 patients with mild symptoms of COVID-19 and at least one risk factor for disease progression were included
- o Patients were randomized to receive a single dose of sotrovimab 500mg IV compared to placeb
- o Most patients were younger (<50) and had one single chronic condition, with obesity being the most prevalent comorbidity
- o 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
- o 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.
- o Hospitalizations were consistent with progressive COVID-19 requiting oxygen support and hospital-level care; only 1 hospitalization was not COVID-related
- o Secondary outcome results demonstrated that sotrovimab significantly reduced progression to severe/critical respiratory COVID-19 compared with placebo (1 vs. 5% p=0.002)
- o Sotrovimab did not reduce length of stay or ICU-bed-days
- o 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 recommendations 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:

- o 910 unvaccinated patients with mild-moderate COVID-19 presenting within 7 days of symptom onset were assigned in a 1:1 fashion to received tixagevimab/cilgavimab 600mg IM x 1 dose or placebo
- o The primary endpoint was COVID-19 hospitalization or death from any cause through day 29
- o 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
- o 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
- o The absolute risk reduction was 4.5% (95% CI 1.1–8.0; p<0·0001), for a number needed to treat of 22
- o Tixagevimab/cilgavimab was generally well tolerated and no differences between it and placebo were observed (29% vs. 36%)
- o 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. The mechanism of action of the drug has been scrutinized by regulators for the theoretical fear of promoting emergence of variants of concern due to promoting mutations as well as reproductive safety.

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

- o 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
- o The primary endpoint was all cause hospitalization or mortality within 29 days
- o 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
- o In that analysis, 28/385 (7.3%) of patients on active treatment experienced the primary outcome, vs. 53/377 (14.1%) who received placebo, for an ARR of 6.8%. Trial recruitment stopped, but there were still another ~600 patient who were undergoing 29-day follow-up.
- o In the final analysis published in December 2021, it was 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
- o 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 as also not statistically significant
- o Data from the FDA reveal that during the second half of the study, the event rate was numerically higher in the molnupiravir arm than the placebo arm (20 vs. 15 events, respectively).

- o The primary outcome appeared to be driven by very high event rates (>20%) that were apparent in countries like Brazil, whereas 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 abovementioned 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, as well as 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 are necessary. Overall, the uptake of the drug 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, as well as lack of robust safety data, guidelines (e.g., IDSA) do not recommend the use of fluvoxamine outside of 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. There were also additional concerns posed about the lack of full safety evaluation with this dose. The recommended starting dose in patients over 55 years old is 25mg daily, whereas the trial's dosing is 8 times that dose. As fluvoxamine can cause a variety of 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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