

Doctors of BC Town Hall: Prescribing Therapies for Mild-Moderate COVID-19

February 9, 2022

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We gratefully acknowledge that we are gathered on the unceded, traditional, and ancestral lands of First Nations in this place currently known as British Columbia where we work, play and live. First Nations have been responsible for stewarding this land for all time and we give thanks

as uninvited guests on these lands.



- 1. What new treatment options are available, evidence, and challenges (i.e., contraindications and interactions, side effects)?
- 2. Who are the patients who will most benefit?
- 3. What might a step-by-step assessment look like?
- 4. What's our approach to implementation in BC?
- 5. Next steps for you

What is nirmatrelvir/ritonavir (Paxlovid)?

- Protease Inhibitor (PI) specific to SARS-COV-2
- Active against all variants of concern, including Omicron
- No measurable activity against human proteases; genotoxicity and mutagenicity not observed; similar side-effects to other PIs
- Extensively metabolized by CYP 3A4
 - T1/2 = 2hrs alone; extended by ritonavir
 - Nirmatrelvir is renally excreted
- 150mg/100mg nirmatrelvir/ritonavir tabs
 - 2 tabs/1 tab (300mg/100mg) PO BID
 - Kit contains 30 tabs
 - Renally adjusted for eGFR 30-60m/min
 - 150mg/100mg PO BID







Studying this medication: EPIC-HR Study

- Not published as of today; Health Canada issued a full Notice of Compliance
- Randomized, double-blind placebo-controlled trial
 - Conducted globally (41% participants from the US); 95% Delta VoC
 - Unvaccinated adults with mild-moderate COVID-19 at high-risk of progression
 - Age \geq 60 or an at-risk condition (obesity, current smoker, heart disease, diabetes)
 - Randomized within 3 days of symptom onset, increased to 5 days after \sim 1/3 of ppt enrolled
- Primary end-point: 89% RRR; 5.8% ARR and NNT 17

| Efficacy outcome results | | | | | |
|---|---|---|----------|--|--|
| Patients with COVID-19-related hospitalisation or death from any cause through Day 28 | | | | | |
| | PF-07321332; ritonavir | Placebo | P-value | | |
| Primary endpoint Treatment within 3 days of symptom onset, n (%) | 5/697 hospitalised with no deaths (0.7%) | 44/682 hospitalised with 9 subsequent deaths (6.5%) | p<0.0001 | | |
| Secondary endpoint Treatment within 5 days of symptom | 8/1039 hospitalised with no deaths (0.8%) | 66/1046 hospitalised with 12 subsequent deaths (6.3%) | p<0.0001 | | |

Source: Pfizer

Considerations/challenges with nirmatrelvir/ritonavir

- No peer-reviewed publication to critically appraise as of Feb 9, 2022
 - Who was excluded from the trial?
 - Treatment discontinuations
 - All-cause hospitalizations and all-cause mortality
- Recommendations are conditional and subject to change
- Trial conducted during Delta wave; generalizability to Omicron/BC
- Various contraindications more real-world evidence is needed
- Very challenging drug-drug interactions
 - Many common drug classes, e.g., antiarrhythmics, anticoagulants, antiplatelet agents, statins, antipsychotics, opioids like fentanyl and methadone
 - Some can be managed but require additional steps
 - Check multiple resources, modify current therapy, consult, follow-up

What is sotrovimab (Xevudy)?

- Monoclonal antibody against spike protein
 - Large binding domain; maintained activity against Omicron
- Dosed 500mg IV x 1 dose IV infusion over an hour plus observation
- Evaluated in a randomized, double-blind placebo-controlled trial (COMET-ICE); similar to EPIC-HR (except all-cause primary endpoint)

| Table 2. Efficacy Outcomes through Day 29 (Intention-to-Treat Population).* | | | | | |
|---|-------------------------|----------------------|--|--|--|
| Outcome | Sotrovimab (N = 291) | Placebo (N = 292) | | | |
| Primary outcome | | | | | |
| Hospitalization for >24 hr for any cause or death from any cause — no. (%) | 3 (1) | 21 (7) | | | |
| Hospitalization for >24 hr for any cause | 3 (1) | 21 (7) | | | |
| Death from any cause | 0 | 1 (<1)† | | | |

Considerations/challenges with sotrovimab?

- Well-tolerated with few contraindications and no DDI
- Infusion time and operational challenges (e.g., location, IPC issues, staffing)
- High-cost therapy comparatively
- Unclear evidence for those who are immuno-competent or vaccinated as patients have or produce their own antibodies; data in seropositive patients is mixed
- Potential for resistance could emerge as seen with other mAbs



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BC's COVID-19 Clinical Therapeutics Committee (CTC) Recommendations

- Published on BCCDC Website
- <u>Conditional Recommendation</u> for nirmatrelvir/ritonavir (Paxlovid) awaiting peer review evidence
- Search: BCCDC COVID-19 Therapeutics

Clinical Practice Guide: Recommendations and Evidence -

new February 1, 2022

 Therapy Recommendations

 Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days is recommended within 5 days of symptom onset

 (CONDITIONAL RECOMMENDATION pending peer-reviewed publication)

 Nirmatrelvir/ritonavir roll-out is gradual. Check with leadership if it can be used in your treatment setting (e.g., in-hospital, LTC)

 OR, if drug-drug interactions or contraindications prohibit administration (See Practice Tool 3 – Drug Interactions and Contraindications)

 Sotrovimab 500mg IV x 1 dose is recommended within 7 days of symptom onset as an alternative to nirmatrelvir, in cases where IV administration is feasible

Evidence for Multivariable Inclusion Criteria



| 0 at-risk conditions < | <20 | 0.40/ | | | |
|--------------------------|-------|-------|-------|-------|-------|
| 2 | | 0.4% | 0.2% | 0.1% | 0.0% |
| | 20-39 | 1.8% | 0.7% | 0.4% | 0.2% |
| 4 | 40-49 | 2.3% | 0.8% | 0.5% | 0.3% |
| 5 | 50-59 | 3.2% | 1.2% | 0.8% | 0.4% |
| 6 | 50-69 | 3.6% | 1.3% | 0.8% | 0.4% |
| 7 | 70-79 | 6.3% | 2.2% | 1.5% | 0.7% |
| 8 | 30+ | 11.8% | 4.0% | 2.7% | 1.3% |
| 1-2 at-risk conditions < | <20 | 1.2% | 0.4% | 0.3% | 0.1% |
| 2 | 20-39 | 4.7% | 1.8% | 1.1% | 0.6% |
| 4 | 40-49 | 5.9% | 2.2% | 1.3% | 0.7% |
| 5 | 50-59 | 8.3% | 3.2% | 1.9% | 1.0% |
| 6 | 50-69 | 9.5% | 3.6% | 2.2% | 1.1% |
| 7 | 70-79 | 17.2% | 6.9% | 4.2% | 2.0% |
| 8 | 30+ | 33.9% | 13.1% | 8.1% | 3.9% |
| 3+ at-risk conditions < | <20 | 7.3% | 1.8% | 1.4% | 1.4% |
| 2 | 20-39 | 25.2% | 11.0% | 6.6% | 3.6% |
| 4 | 40-49 | 35.6% | 8.3% | 6.5% | 4.0% |
| 5 | 50-59 | 37.0% | 12.3% | 8.9% | 5.1% |
| 6 | 50-69 | 40.3% | 16.2% | 9.4% | 5.0% |
| 7 | 70-79 | 59.6% | 26.6% | 15.9% | 7.5% |
| 8 | 30+ | 83.7% | 43.8% | 26.3% | 12.7% |

BC-specific modeling; Omicron wave. BCCDC/HSAIR

Focus: those with the most likelihood of benefit

Highest-risk individuals (~15% progression to severe illness)

Who is the treatment currently being considered for?

Refer to: Practice Tool #1- Assessment Steps and Practice Tool #2- CEV Definitions

Patients who test positive for COVID-19 via a Polymerase Chain Reaction (PCR) or Rapid Antigen Test (RAT) test

AND

Have been identified as being at increased risk for needing to go to the hospital for COVID-19:

- Immunocompromised individuals identified as Clinically Extremely Vulnerable (CEV) Group 1 and Group 2 (CEV 1 and CEV 2), regardless of vaccine status or previous infection
 - Not all children ages 12-17 who are CEV 1 or 2 will benefit from treatment. Those with multiple co-morbidities would have the highest benefit
- Unvaccinated or partially vaccinated individuals with high-risk conditions identified as CEV 3
- Unvaccinated or partially vaccinated individuals:
 - \circ aged \geq 70 years with one or more chronic condition/co-morbidity
 - \circ aged \geq 60 years with three or more chronic conditions/co-morbidities
 - aged \geq 60 years who are Indigenous

Unvaccinated or partially vaccinated refers to the receipt of 0, 1 or 2 vaccine doses. Two doses of vaccine is considered partially vaccinated for these treatments.

Considerations/challenges

- Assessing risk
- Symptom severity
- Symptom trajectory
- Symptom window





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Step-by-step Clinical Assessment

- Omicron is highly variable in its clinical presentation
- Detailed assessment of risk factors:
 - Age-associated risk
 - Immunocompromise CEV 1 and 2
 - Vaccine status
 - Comorbidities type and number
 - Clinical Status symptoms, severity, trajectory

Practice Tool #1: Step-by-Step Assessment for Clinicians new February 1, 2022

 This guide is a step-by-step clinical assessment tool for clinicians such as nurses or physicians who are directly involved in assessment and management of patients with mildmoderate COVID-19.

Assess Immunity: CEV 1 and 2

- Unable to mount a response to vaccine humoral immunity
- Weak underlying immunity innate immunity
 - A. Transplant
 - B. Active Chemotherapy
 - C. Severe primary immune deficiency syndromes
 - D. Potent immune suppression anti-CD-20; B cell depleting
 - E. Other MAB's
 - F. High dose steroids
 - G. MMF, cyclophosphamide, MTX

<u>Practice Tool #2: Definitions of Clinically Extremely Vulnerable</u> (<u>CEV</u>) - new February 1, 2022

Assess Vaccine Status

• Number of doses

For CEV1 and 2: can be offered treatment regardless of vaccine status
For the other high-risk populations: "inadequate" vaccination is less than 3 doses

• Type

o mRNA, viral vector, out-of-country vaccines

• Timing

• How long since the last dose?

o Immunosuppression while vaccinated?

• Previous infection

 \circ May not confer protection against re-infection but the risk of hospitalization is low

Assess Co-morbidities

- Dramatic impact on risk
- Pulmonary disease
- DM on Insulin
- Dialysis and stage 5 CKD
- Mild-mod immunocompromise
- Many others CHF, stroke, obesity, neuromuscular, smoking, frailty
- Use thermal chart in decision making with patients (in Practice Guide)

Use thermal chart to assist further with risk assessment:

| # of at-risk conditions | Age group | 0 Doses | 1 Dose | 2 Doses | 3 Doses |
|----------------------------|-----------|---------|--------|---------|---------|
| 0 at-risk conditions | <20 | 0.4% | 0.2% | 0.1% | 0.0% |
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| | 70-79 | 6.3% | 2.2% | 1.5% | 0.7% |
| | 80+ | 11.8% | 4.0% | 2.7% | 1.3% |
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Assess Clinical Syndrome (symptoms)

Mild to Moderate Disease – symptomatic but <u>not</u> <u>needing O₂ therapy</u>

Severity types simplified:

- 1. "Cold" sore throat, HA, congestion
 - Very mild 2-3 day illness for most vaccinated patients
- 2. "Flu" severe HA, fever, myalgias, N/V, diarrhea
 - May be nearly bedridden
- 3. "Pneumonia/LRTI"- dyspnea, SOBOE, cough
 - May still not need O2

Do not treat asymptomatic patients

Also consider symptom *trajectory* and symptom *window*

- Those who are visibly improving on their own
- Role for observation if early, mild, or improving
- Time for drug transport can be added to the symptom window for patients from rural/remote communities

Patient examples – both meet criteria

- 74 y/o SOD 4
- 2 mRNA vaccines
- DM, HTN, CHF, COPD
- HA, fever, myalgia, cough
- Not improving/worsening
- ≻High Risk
- ➢Offer Treatment

- 48 y/o Ulcerative Colitis SOD 4
- 2 mRNA vaccines
- Infliximab and MTX
- Mild illness congestion, sore throat
- Day 4 of symptoms resolving
- Meets criteria but Low riskOffer Reassurance, monitor

Resources: Clinical Practice Guide and Tools on BCCDC website

<u>Clinical Practice Guide: Recommendations and Evidence</u> new February 1, 2022

Practice Tool #1: Step-by-Step Assessment for Clinicians new February 1, 2022

<u>Practice Tool #2: Definitions of Clinically Extremely Vulnerable</u> (<u>CEV)</u> - new February 1, 2022

Practice Tool #3: Drug-Drug Interactions and Contraindications updated February 3, 2022





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Principles for implementation across BC

Provincial approach with equity

• All geographic regions have a plan and strive for equity in partnership with First Nations Health Authority.

Reach most-at-risk patients

• Strive for patients most at risk of the outcomes to receive the doses.

Safety in prescribing

• Thorough review of patients' medications and medical histories needed, especially given that we, like the rest of the world, are learning about this new medication.

Evidence-informed

• Watching for more international evidence and gathering our own evidence/evaluation

Foundational supports

- Medication supply
- Medication distribution plan
- CTC guidance and clinical decision tools posted on BCCDC
- A common special prescription form (not special authorization) which will also assist with monitoring and evaluation
- Opportunities to learn/webinars/academic detailing for physicians and pharmacists
- Mechanisms to serve unattached patients
- Increasing outpatient capacity for infusions in each health authority (for sotrovimab)
- Evaluation/ ongoing evidence review (especially via the CTC)

Why undertake a staged implementation?

- Reach patients with the highest risk/likelihood of benefit
- Providers (physicians and pharmacist): Given an opportunity to learn about these new therapeutics
- Development of physician and pharmacy expertise/"super-user" to support all providers
- Quickly widening supports for all physicians/NP's to prescribe safely (including pharmacy consultation services, development of
- In the background:
 - Recognition that we are awaiting final peer-reviewed papers
 - Awaiting additional supply to the provinces

Staged approach to implementation

Wave 1: (started the week of January 31)

Infectious disease led teams in each HA – proactive outreach to PCR positive patients BC Renal, BC Cancer, BC Transplant, and Cystic Fibrosis Care BC enabled and linked. FNHA connected to receive support from health authorities as required.

Wave 2: (Goal: week of February 14th) Long Term Care Emergency Departments

Wave 3: (Goal: week of February 21 or earlier) COVID Antiviral Therapeutics e-team (CATe) (Services BC, 8-1-1)

Wave 4: (Goal TBD - ? End of February/Early March) Community family physicians and nurse practitioners



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What does this mean for us as providers at this time? What are our next steps?

- Increased and ongoing need for evidence
 - Available resources (as per previous slides) (BCCDC website CTC tools)
 - Will continue to also push news of new evidence
- For your high-risk patients planning discussions and review
 - For PCR positive patients
 - Wave 1 proactive outreach
 - Will shift in the weeks to come
 - For **RAT positive** patients
 - As patients reach out to you... Screening and assessing
 - HA contacts ID led teams
- Additional supports to watch for: Pharmacy consultation support, CATe service providers as resources, DDI tools... and more...
- Feel prepared to prescribe: Online resources, take advantage of PAD if your group wishes
- Watch communication channels: Commitment to communicate as we move through the subsequent implementation waves quite quickly: DOBC, College, HA communications

Further education

pad Education sessions for Clinicians

For more information on nirmatrelvir/ritonavir:

- BC PAD service is providing additional education sessions via ZOOM focussing on eligibility criteria and drug-drug interaction management
- To schedule: email <u>PAD@gov.bc.ca</u>
- Provide:
 - contact name, email, phone number
 - 3 possible dates & times
 - Approximate group size (max. 100)
 - Your group's specialty area



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- 6. Questions!?