



Coronavirus COVID-19

BC Centre for Disease Control | BC Ministry of Health

Clinical Reference Group Recommendations: Therapies for COVID-19

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The British Columbia COVID-19 Therapeutics Committee (CTC) meets weekly to discuss the most current research on the use of therapies in the management of COVID 19.

Position Statement on Therapies for COVID-19:

“Evidence for the role of various therapies for the prevention or treatment of COVID-19 is quickly emerging and represents a rapidly evolving area of research. Since all agents have the possibility of associated harm, and pharmaceutical supply chains are fragile, it is essential that therapies are used in an evidence-based fashion. With a focus on knowledge translation, it is recommended that all clinical studies are critically appraised for quality and generalizability, and a decision to use any treatment is made in the context of provincially harmonized best practices and patients’ informed consent. It is recognized that compassionate use of drugs may be pursued based on extrapolated or preliminary data or where data is lacking. Ideally, use of such agents would be through participation in a controlled clinical trial to better inform practice. In the absence of research studies or definitive results, patients should be aware of the risks and benefits of novel therapies, and efficacy and safety data collected to inform the larger community.”

*Position statements provide information/direction and express or clarify intent on a particular matter. They are intended as guidance for stakeholders in areas where events are evolving or changing rapidly, the implementation of processes and procedures may be premature, or it is timely to communicate the intent before or as policies and procedures are developed.

While positive results for a small number of treatments are being published, the efficacy, safety and role in therapy for most pharmacological treatments for COVID-19 remain unknown. Currently, international bodies such as the World Health Organization (WHO), recommend that unproven pharmacological therapies for COVID-19 not be used outside of clinical trials. **Within British Columbia, the use of unproven COVID-19 drug therapies outside of clinical trials is NOT recommended.** Participation in clinical trials allows for ethical evaluation of the efficacy and safety of potential agents, minimizes inconsistencies in usage that is harmful to the clinical community and the public, and protects the drug supply chain. It is recognized that there may be extenuating individual circumstances where clinicians decide to use such therapies when clinical trials are unavailable. In settings **where unproven therapies are used, the WHO has**

If you have fever, a new cough, or are having difficulty breathing, call 8-1-1.



provided a standardized case report form for data collection to ensure that there is contribution to scientific research and the clinical community.

In circumstances where practice-changing results become available, such data should be carefully interpreted with particular attention to effect size, applicability, safety and practical issues of incorporating the evidence into practice that are specific to patients in British Columbia. The recommendations listed below have been written with careful consideration of these points.

For recommendations pertaining to Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 please visit BCCDC website at:

http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID19_MIS-C_ClinicianGuidance.pdf

Recommendations for Specific Therapies

1. Corticosteroids

i) Non hospitalized patients with no oxygen requirements:

In adults with mildly ill COVID-19 aged 65 and over OR aged 50 and over with underlying health conditions and within 14 days of symptom onset, **inhaled budesonide** 800 µg twice daily for 14 days may be considered on a case by case basis in discussion with the patient by clearly highlighting the uncertainty in the benefit of treatment, and the risks and potential adverse effects. Informed consent should be obtained and treatment initiated as soon as possible. Underlying health conditions include weakened immune system due to illness or medication; heart disease and/or hypertension; chronic lung disease; diabetes; hepatic impairment; stroke or other neurological condition; obesity or BMI above 35.

ii) Hospitalized patients requiring oxygen or higher levels of respiratory support

Dexamethasone 6 mg IV/PO q24h for up to 10 days is strongly recommended (RECOVERY trial), unless higher doses are clinically indicated (e.g. asthma exacerbation, refractory septic shock, history of chronic steroid use, obstetric use for fetal lung maturation).

Hydrocortisone 50 mg IV q6h is recommended as an alternative (REMAP-CAP trial). If dexamethasone and hydrocortisone are not available, methylprednisolone 32 mg IV q24h or prednisone 40 mg PO daily are recommended.

2. TL-6 blockers/Biologics/Small molecules (Tocilizumab, Sarilumab, Baricitinib)

Tocilizumab 400mg IV (single dose) or sarilumab 400mg IV (single dose) is recommended (REMAP-CAP and RECOVERY) for patients requiring life support due to confirmed COVID-19. This includes high-flow oxygen support (e.g., Optiflow) if flow rate > 30 L/min and FiO₂ > 0.4 OR invasive or non-invasive ventilation OR vasopressor or inotropic support. Tocilizumab or sarilumab must be administered within 24 hours of the initiation of life support measures. Patients admitted to hospital for more than 14 days with symptoms of COVID-19 should not receive tocilizumab or sarilumab for this indication. Tocilizumab or sarilumab should only be initiated when life support is required because of COVID-19 rather than other causes (such as bacterial infection, pulmonary embolism, etc.).

If tocilizumab is not available due to ongoing global shortages, baricitinib is recommended as an alternative.

Baricitinib 4 mg po daily (for patients with GFR ≥ 60 mL/min) or 2 mg po daily (for patients with GFR 30-59 mL/min) or 2 mg po every 2nd day (for patients with GFR 15-29 mL/min) up to 14 days, or until discharge from hospital (whichever occurs first) is recommended (COV-BARRIER) for patients requiring life support due to confirmed COVID-19. This includes high-flow oxygen support (e.g., Optiflow) if flow rate > 30 L/min and FiO₂ > 0.4 OR invasive or non-invasive ventilation OR vasopressor or inotropic support. Baricitinib should be administered within 24 hours of the initiation of life support measures. Baricitinib should only be initiated when life support is required because of COVID rather than other causes (such as bacterial infection, pulmonary embolism, etc). Baricitinib should not be administered to patients with neutrophils <

1.0 giga/L, lymphocytes < 0.2 giga/L, ALT or AST > 5 x ULN, or eGFR < 15 mL/min (or receiving renal replacement therapy).

*There are very limited data on baricitinib in pregnancy. Risks and benefits of baricitinib should be discussed on a case by case basis with pregnant women with severe COVID-19.

Tocilizumab is **not** recommended for patients receiving low-flow oxygen support. The RECOVERY trial found a survival benefit of 4% (tocilizumab 29% vs. usual care 33% 28-day mortality) in patients who had CRP \geq 75 mg/L AND low-flow oxygen, non-invasive respiratory support, or invasive mechanical ventilation. However, considering the scarcity of IL-6 blockers in Canada, drug therapy should be prioritized to the persons with both the highest need and the greatest likelihood of benefiting from the therapy. Combined with outstanding issues in the preliminary findings of the RECOVERY trial (e.g. 17% of patients randomized to tocilizumab not receiving the drug), the CTC recommends prioritizing tocilizumab use only for critically ill patients at this time, which is the population shown to benefit in both the REMAP and RECOVERY trials.

3. Therapeutic anticoagulation and Venous Thromboembolism (VTE) prophylaxis

i) Hospitalized patients requiring low-flow oxygen:

Therapeutic anticoagulation (LMWH preferred) may be beneficial and therefore considered in patients without high risk features* for serious bleeding and NOT requiring organ support. If used, anticoagulation for COVID-19 should start within 72 hours of admission and continue for 14 days or until hospital discharge. Patients who decompensate and require organ support while on therapeutic anticoagulation should continue on therapeutic anticoagulation. Therapeutic anticoagulation was superior to standard of care for composite 21-day organ support free survival in the ATTACC/ACTIV-4a/REMAP-CAP trials. Benefits appear to be driven by reducing progression to high-flow oxygen, non-invasive ventilation, or vasopressors. There was insufficient certainty on whether therapeutic anticoagulation improves mortality or intubation. Therapeutic anticoagulation reduces thrombotic events (1.4% vs 2.7%) but may increase major bleeding (1.9% vs 0.9%). *High risk features for bleeding include: age 75 or greater, eGFR less than 30 mL/min, any coagulopathy, platelet count less than 50, use of dual antiplatelet therapy, recent history of serious GI bleed or recent intracranial condition (stroke, neurosurgery, aneurysm, cancer), epidural or spinal catheter.

ii) Hospitalized patients requiring organ support (high-flow oxygen, noninvasive ventilation, mechanical ventilation and/or vasopressor/inotropic support)

Prophylactic-intensity dosing of low molecular weight heparin (LMWH) is recommended for VTE prophylaxis in patients who do not have suspected or confirmed VTE (or other indications for therapeutic anticoagulation). There is a high probability of harm when therapeutic anticoagulation is initiated in patients who have received organ support for greater than 48 hours (n=1074; NIH mpRCT). **Patients receiving therapeutic anticoagulation for COVID-19 prior to organ support should REMAIN on therapeutic anticoagulation and continue for up to 14 days or until hospital discharge.**

4. Colchicine

In outpatients aged 40 years or older with PCR-confirmed COVID-19 who have at least one risk factor† and no contraindications††, colchicine 0.6 mg PO BID x 3 days, then 0.6 mg daily x 27 days may be considered on a case-by-case basis in discussion with the patient by clearly highlighting the uncertainty in the benefit of treatment, and the risks and potential adverse effects. Informed consent should be obtained and treatment initiated as soon as possible.

5. Remdesivir

Remdesivir has not demonstrated benefit in survival, progression to ventilation or length of hospital stay and remains uncertain with respect to shortening time to recovery by 5 days. The World Health Organization (WHO) has issued a conditional recommendation against the use of remdesivir in hospitalized COVID-19 patients. Further evaluation in approved clinical trials is strongly encouraged. If remdesivir is used outside of clinical trials, full disclosure of risks and benefits with consideration of patient values and preferences are necessary, as it is not considered standard of care. Furthermore, it should be restricted to hospitalized patients requiring supplemental oxygen but not requiring non-invasive or invasive mechanical ventilation.

6. Lopinavir / Ritonavir (Kaletra®)

Lopinavir/ritonavir is not recommended for treatment of COVID-19. Lopinavir/ritonavir is not recommended for prophylaxis of COVID-19 outside of approved randomized-controlled trials.

7. Chloroquine or Hydroxychloroquine

Chloroquine or hydroxychloroquine (with or without azithromycin) is not recommended for treatment or prophylaxis of COVID-19.

8. Oseltamivir

Oseltamivir is not recommended for treatment or prophylaxis of COVID-19.

9. Ribavirin and Interferon

Interferon IV/SC is not recommended for the treatment of COVID-19. Ribavirin/Interferon (Inhaled) is not recommended outside of approved clinical trials.

10. Ivermectin

Ivermectin is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

11. Ascorbic Acid and Vitamin D

Ascorbic acid and Vitamin D are not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

12. Convalescent Plasma[#]

Convalescent plasma[#] is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

13. Intravenous Immunoglobulin G

Intravenous immunoglobulin G (IVIG) is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

14. Monoclonal Antibodies/Antibody Cocktails

i) Critically ill:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) are NOT recommended. An RCT of REGN-COV2 in this population was halted due to signals of harm. Regdanvimab conditions for use state that it may be associated with worse outcomes in the critically ill. RECOVERY showed no benefit in the subgroup that required organ support. Various guidelines (IDSA, NIH, INESSS) recommend against mAbs in this setting.

ii) Severely ill:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) are not recommended. MAbs have shown inconsistent results in RCTs. TICO was stopped for futility as mortality was numerically higher in the Bamlanivimab arm. RECOVERY demonstrated a mortality benefit with REGN-COV2, but only in seronegative patients, with signals of harm in seropositive patients. Reliable rapid antibody tests to identify the target population are not readily available and all mAbs remain unapproved in Canada for in-patients with COVID-19.

iii) Mildly ill:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) IV have shown to reduce hospitalization rates (although not mortality or length of stay) in UNVACCINATED outpatients at high-risk of complications due to comorbidities (age >40 with a comorbidity like obesity or hypertension). Due to high vaccination rates and barriers to operationalizing outpatient IV administration outside of clinical trials, the clinical application of these studies is limited. **mAbs may be considered on a case-by-case basis in those inadequately immunized (unimmunized, partially immunized or inadequate immune response) with mild disease AND who are at high risk of developing severe COVID-19-related complications.** The subcutaneous route has shown similar reductions in viral loads, but clinical data is lacking and would still present operational barriers such as multiple injections and required observation time.

iv) Prophylaxis:

Bamlanivimab/etesevimab IV has shown to reduce the development of symptomatic COVID-19 as prophylaxis in unvaccinated LTC residents, as has subcutaneous REGN-COV2 given to unvaccinated, seronegative, PCR-negative household contacts if given within 96 hours of exposure. Due to lack of reliable rapid tests to identify the target population within the prophylaxis window, lack of impact on hospitalization rates or mortality and low generalizability of these studies, **mAb administration is not recommended for post-exposure prophylaxis.**

15. Antibiotics

Antibiotics should be initiated based on local institutional antibiograms and sensitivities if bacterial infection is suspected.

16. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Acetaminophen is recommended preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.

17. Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs)

Patients on ACE inhibitors and ARBs are recommended to continue these agents as indicated and not cease therapy solely on the basis of COVID-19.

18. SSRIs

SSRIs are not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

19. Other investigational therapies

Other investigational agents including arbidol, ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab, famotidine, niacin, thymosin, natural health products and traditional Chinese medicines are not recommended for treatment or prophylaxis of COVID-19 due to lack of data, lack of availability, or both.

Denotes that a clinical trial of named therapy is currently planned or underway in British Columbia. Links below for registered trials in Canada and British Columbia.

Canada:

<https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-clinical-trials/list-authorized-trials.html>

British Columbia:

<https://bcahsn.ca/covid-19-response/inventory/>

***Recommendations are consistent with guidelines from the World Health Organization (WHO), the Surviving Sepsis Campaign (SSC) (a joint initiative of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)), the Public Health Agency of Canada (PHAC), the Canadian Critical Care Society (CCCS), the Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and The Australian and New Zealand Intensive Care Society (ANZICS)**

†Age ≥ 70 years, obesity (BMI ≥ 30 kg/m²), diabetes, hypertension (systolic ≥ 150 mmHg), respiratory or coronary disease, heart failure, fever $\geq 38.4^{\circ}\text{C}$, and dyspnea.

†† Contraindications – GFR < 30 mL/min, inflammatory bowel disease, chronic diarrhea or malabsorption, neuromuscular disease, severe liver disease, chemotherapy, current colchicine treatment, hypersensitivity to colchicine, or concurrent medications that interact with colchicine (e.g. amiodarone, azoles, carvedilol, cyclosporine, estradiol, macrolides, propafenone, protease inhibitors, quinidine, quinine, verapamil).

About the Clinical Reference Group

*The Clinical Reference Group (CRG) is made up of senior individuals from relevant healthcare areas (including critical care, epidemiology, infectious disease, microbiology, public health, and clinical specialties) acting as a collective resource for current COVID-19 knowledge. They provide clinical advice and guidance to support the overall work being done by the BC Centre for Disease Control, the Provincial Health Office, and the Ministry of Health. The CRG includes representation from the provincial health authorities and works with the other Ministry areas in order to provide cross-input on all COVID-19 content.