British Columbia COVID-19 Therapeutics Committee (CTC) and COVID-19 Therapeutics Review and Advisory Working Group (CTRAWG) Clinical Practice Guidance for

Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19

SUMMARY
last updated November 26th, 2021

Recommendations in this document apply to adults 18 years of age or older.

This document is dynamic and addresses key therapeutic areas of concern for clinicians. The complete and most up-to-date version of the guidelines is available at http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments

Specialist consultation (e.g., Critical Care, Infectious Disease, Hematology, or Rheumatology) is recommended if any investigational treatment is offered to a patient with COVID-19 outside of approved clinical trials. Informed consent should be obtained from the patient or the substitute decision maker.

SEVERITY OF ILLNESS	ANTIVIRAL THERAPY	ANTIBACTERIAL THERAPY	IMMUNOMODULATORY THERAPY	OTHER THERAPEUTICS
Critically Ill Patients *Hospitalized, ICU-based* Patients requiring respiratory support (high-flow oxygen, noninvasive ventilation, mechanical ventilation) and/or vasopressor/ inotropic support	**Chloroquine** or **Hydroxychloroquine** is **not** recommended for the treatment of COVID-19 **Lopinavir/ritonavir** is **not** recommended for the treatment of COVID-19 **Remdesivir** is **not** recommended outside of approved clinical trials **Interferon IV/SC** is **not** recommended for the treatment of COVID-19. **Ribavirin/ Interferon (Inhaled)** is **not** recommended outside of approved clinical trials **Based on the current scientific evidence and best-practice guidelines, the College of Physicians and Surgeons of BC, the College of Pharmacists of BC, the BC College of Nurses and Midwives and the CTC do not approve of the use of ivermectin for either treatment or prophylaxis for COVID-19 and BC registrants must not prescribe it for this purpose. Ivermectin** should **not** be used outside of approved clinical trials.	**Ceftriaxone 1-2 g IV q24h x 5 days** is recommended if there is concern for bacterial co-infection (alternative for severe beta-lactam allergy: moxifloxacin 400 mg IV q24h x 5 days) **Azithromycin 500 mg IV q24h x 3 days** is recommended if atypical bacterial infection is suspected (not required if on moxifloxacin) De-escalate on the basis of microbiology results and clinical judgment	**Dexamethasone 6 mg IV/SC/PO q24h for up to 10 days** is **strongly recommended** (RECOVERY trial), unless higher doses are clinically indicated.* 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. **Tocilizumab 400 mg IV (single dose)** OR **Sarilumab 400 mg IV (single dose)** is **recommended** (REMAP-CAP, 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/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/Sarilumab for this indication. Tocilizumab/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. **Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGEN-COV, Sotrovimab, Regdanvimab)** are **NOT** recommended. An RCT of REGEN-COV in this population was halted due to signals of harm. Regdanvimab and REGEN-COV 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. **Convalescent Plasma** is **not** recommended for the treatment of COVID-19 **IVIG, Colchicine and other biologics (Anakinra** are **not** recommended outside of approved clinical trials.	**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. **ACE inhibitors** and **ARBs** should not be discontinued solely on the basis of COVID-19 **NSAIDs** should not be discontinued solely on the basis of COVID-19
Severely Ill Patients *Hospitalized, ward-based, long-term care* Patients requiring supplemental oxygen therapy	**Chloroquine** or **Hydroxychloroquine** is **not** recommended for the treatment of COVID-19 **Lopinavir/ritonavir** is **not** recommended for the treatment of COVID-19 **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. **Interferon IV/SC** is **not** recommended for the treatment of COVID-19. **Ribavirin/ Interferon (Inhaled)** is **not** recommended outside of approved clinical trials **Based on the current scientific evidence and best-practice guidelines, the College of Physicians and Surgeons of BC, the College of Pharmacists of BC, the BC College of Nurses and Midwives and the CTC do not approve of the use of ivermectin for either treatment or prophylaxis for COVID-19 and BC registrants must not prescribe it for this purpose. Ivermectin** should **not** be used outside of approved clinical trials.	**Antibacterial therapy** is **not** routinely recommended outside of approved clinical trials unless other indications justify its use (e.g., suspected bacterial co-infection in COVID-19 positive patients)	**Dexamethasone 6 mg IV/SC/PO q24h for up to 10 days** is **strongly recommended** (RECOVERY trial), unless higher doses are clinically indicated.* 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. **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 >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. **Monoclonal antibody combination REGEN-COV 2.4g (casirivimab 1.2g + imdevimab 1.2g) x 1 dose is recommended** (RECOVERY trial) in seronegative patients if given within 10 days of symptom onset, irrespective of COVID-19 vaccine status to reduce mortality. Serology turn-around time must be considered when assessing the window of opportunity for REGEN-COV. If the patient is deteriorating to critically ill AND is very likely to be seronegative due to being unimmunized, partially immunized or have inadequate immune response (#), REGEN-COV can be given without serostatus results. **Convalescent Plasma** is **not** recommended for the treatment of COVID-19. **IVIG, Colchicine and biologics (Anakinra, Baricitinib)** are **not** recommended outside of approved clinical trials.	**Therapeutic anticoagulation (LMWH preferred) may 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. **ACE inhibitors** and **ARBs** should not be discontinued solely on the basis of COVID-19 **NSAIDs** should not be discontinued solely on the basis of COVID-19
Mildly Ill Patients *Ambulatory, outpatient, long-term care* Patients who do not require supplemental oxygen, intravenous fluids, or other physiological support; may include mildly ill inpatients in outbreak settings	**Chloroquine** or **Hydroxychloroquine** is **not** recommended for the treatment of COVID-19 **Lopinavir/ritonavir** is **not** recommended for the treatment of COVID-19 **Remdesivir#** is **not** recommended outside of approved clinical trials **Interferon IV/SC** is **not** recommended for the treatment of COVID-19. **Ribavirin/ Interferon (Inhaled)** is **not** recommended outside of approved clinical trials **Based on the current scientific evidence and best-practice guidelines, the College of Physicians and Surgeons of BC, the College of Pharmacists of BC, the BC College of Nurses and Midwives and the CTC do not approve of the use of ivermectin for either treatment or prophylaxis for COVID-19 and BC registrants must not prescribe it for this purpose. Ivermectin** should **not** be used outside of approved clinical trials.	**Antibacterial therapy** is **not** routinely recommended outside of approved clinical trials unless other indications justify its use (e.g., suspected bacterial co-infection in COVID-19 positive patients)	**Monoclonal antibody Sotrovimab 500mg IV x 1 dose may be considered** on a case-by-case basis in those unimmunized, partially immunized or who have inadequate immune response (#) with no prior COVID-19 history and mild disease AND who are at high risk of developing severe COVID-19-related complications due to at least one co-morbidity (e.g. obesity, hypertension, kidney disease). Due to low drug availability, supplies may be prioratized to higher risk populations. Sotrovimab must be given within 7 days of symptom onset. In COMET-ICE, sotrovimab has shown to reduce hospitalization rates, although not mortality or length of stay. REGEN-COV has also been evaluated in this setting; however, it is currently being reserved for severely ill patients. **Inhaled budesonide 800 µg twice daily for 14 days may be considered** on a case by case basis 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, 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; **Colchicine** was evaluated at 0.6 mg PO BID x 3 days, then 0.6 mg daily x 27 days in a large Canadian RCT 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. If colchicine is used outside of clinical trials, full disclosure of risks and benefits with consideration of patient values are necessary. **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 enrollment due to futility. If fluvoxamine is used outside of clinical trials, full disclosure of risks and benefits with consideration of patient values are necessary. **Biologics/Small molecules (Tocilizumab, Sarilumab, Anakinra, Baricitinib)** are **not** recommended outside of approved clinical trials **Convalescent Plasma/IVIG** are **not** recommended outside of approved clinical trials.	**ACE inhibitors** and **ARBs** should not be discontinued solely on the basis of COVID-19 **NSAIDs** should not be discontinued solely on the basis of COVID-19
Prophylaxis Asymptomatic patients with known COVID-19 exposure	**Chloroquine** or **hydroxychloroquine** is **not** recommended for prophylaxis in patients with known COVID-19 exposure. **Lopinavir/ritonavir** is **not** recommended outside of approved clinical trials **Based on the current scientific evidence and best-practice guidelines, the College of Physicians and Surgeons of BC, the College of Pharmacists of BC, the BC College of Nurses and Midwives and the CTC do not approve of the use of ivermectin for either treatment or prophylaxis for COVID-19 and BC registrants must not prescribe it for this purpose. Ivermectin** should **not** be used outside of approved clinical trials. Bamlanivimab/etesevimab IV has shown to reduce the development of symptomatic COVID-19 as prophylaxis in unvaccinated LTC residents, as has subcutaneous REGEN-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.**		
Discharge Patients with known COVID-19 that have recovered and are discharged from hospital	No COVID-19 specific medications are recommended on discharge (includes corticosteroids and DVT chemoprohylaxis; unless indicated for other reasons)			

** e.g., asthma exacerbation, refractory septic shock, history of chronic steroid use, obstetric use for fetal lung maturation*

(#) Active treatment for solid tumor or hematological malignancies; solid organ transplant treated with immunosuppression; CAR-T cell therapy or hematopoietic stem cell transplant within the last 2 years; moderate to severe primary immunodeficiency; advanced untreated HIV or AIDS; active receipt of anti-B cell therapies, high-dose systemic steroids (=20mg prednisone equivalent daily for at least 14 days), alkylating agents, antimetabolites or anti-TNF agents

COVID-19 Therapy Review and Advisory Working Group determines allocation of COVID-19 therapies within the province using the Ethical Framework.

Vancouver Coastal Health — Promoting wellness. Ensuring care.
fraserhealth — Better health. Best in health care.
Provincial Health Services Authority — Province-wide solutions. Better health.
Providence Health Care — How you want to be treated.
island health
Interior Health — Every person matters
northern health — the northern way of caring
British Columbia Ministry of Health
BC Patient Safety & Quality Council — Working Together. Accelerating Improvement.
First Nations Health Authority — Health through wellness