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

http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/treatments

SUMMARY
last updated August 29th, 2022

SEVERITY OF ILLNESS	ANTIVIRAL 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	**Remdesivir** 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 treatment or prophylaxis of COVID-19 and BC registrants must not prescribe it for this purpose. Ivermectin** should **not** be used outside of approved clinical trials.	**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. ** e.g., asthma exacerbation, refractory septic shock, history of chronic steroid use, obstetric use for fetal lung maturation* **Tocilizumab, Sarilumab OR Baricitinib is recommended** 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 OR Baricitinib must be administered within 24 hours of the initiation of life support measures. While head-to-hear comparative data are lacking, the magnitude of benefit of both agents appears equivalent. However, more robust data exist to support the use of tocilizumab and sarilumab. Baricitinib also carries the additional challenges related to gastric access and cytotoxic precautions. The ultimate choice of agent depends on patient characteristics and practical considerations. Patients receiving baricitinib prior to becoming critically ill may stop baricitinib and be switched to a one-time dose of an IL-6 inhibitor. There is no evidence to co-administer IL-6 inhibitors with baricitinib. **Tocilizumab 400 mg IV (single dose)** OR **Sarilumab 400 mg IV (single dose)** is **recommended** (REMAP-CAP, RECOVERY). 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). Tocilizumab or sarilumab should not be combined with baricitinib. **OR** **Baricitinib 4 mg po daily** (for GFR ≥ 60 mL/min) **or 2 mg po daily** (for GFR 30-59 mL/min) **or 2 mg po every 2nd day** (for GFR 15-29 mL/min) **up to 14 days**, or until discharge from hospital (whichever occurs first) **is recommended** (COV-BARRIER, RECOVERY). 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). Baricitinib should not be combined with tocilizumab or sarilumab. **Limited data exist 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. **Colchicine and other biologics (e.g., 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. **Antibiotic therapy is not routinely recommended** for the treatment of COVID-19 pneumonia. If bacterial co-infection is suspected, follow local practice guidelines for CAP, HAP and VAP. **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	**Remdesivir** did not initially demonstrate a benefit in survival in the SOLIDARITY trial (9.4% vs. 10.3%) but was shown to slightly reduce mortality (14.6% vs. 16.3%, p=0.03) in the final analysis. The increase in mortality, allowing for a small effect size to be seen was driven by the Delta variant in the second part of the trial. A 10-day course of remdesivir increased the length of hospital stay by 1 day. As mortality in patients with severe COVID-19 has decreased 10-fold in the Omicron wave vs. Delta, the potential impact of remdesivir on mortality is likely minimal. In addition, therapies including baricitinib which lower mortality and progression to ventilation have since been incorporated into the standard of care. If remdesivir is used in severe COVID-19, clinicians need to acknowledge the low probability of a benefit, potential impact on length of stay and drug scarcity. A 5-day course (or until discharge, whichever is sooner) should be used, as it has shown to be non-inferior to the 10-day course. **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 treatment of COVID-19 and BC registrants must not prescribe it for this purpose. Ivermectin** should **not** be used outside of approved clinical trials.	**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. ** e.g., asthma exacerbation, refractory septic shock, history of chronic steroid use, obstetric use for fetal lung maturation* **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. **Baricitinib 4 mg PO daily** (for GFR >60 mL/min), or **2 mg PO daily** (for GFR 30-59 mL/min), or **2 mg PO every 2nd day** (for GFR 15-29 mL/min) **up to 14 days****, or until hospital discharge (whichever occurs first) **is recommended** (COV-BARRIER) for patients hospitalized from COVID-19 requiring supplemental oxygen. Baricitinib should be administered within 24 hours of initiation or change in baseline use of oxygen due to COVID-19 pneumonia (not from other causes such as heart failure, pulmonary embolism, etc.). Considerations for use include certainty of COVID-19 as cause of deterioration, clinical progression, evidence of inflammation (e.g. elevated C-reactive protein ≥ 50 mg/L, ferritin ≥ 1000 µg/L), and potential for adverse effects. Baricitinib should not be administered to patients with neutrophils <1.0 109/L, lymphocytes <0.2 109/L, ALT or AST >5 x ULN, GFR <15 mL/mmin/1.73 m2, or who have been admitted for more than 14 days with symptoms of COVID-19. Patients who received immunosuppressants (high-dose corticosteroids, biologics, or JAK inhibitors) before randomization were excluded from the COV-BARRIER trial; if baricitinib is being considered in these patients, risks and benefits should be discussed on a case-by-case basis. **Limited data exist on baricitinib in pregnancy. Risks and benefits should be discussed on a case-by-case basis with pregnant patients with severe COVID-19* ***Early baricitinib discontinuation should be considered in patients who have clinically improved and no longer require supplemental oxygen* **Monoclonal antibody combination REGEN-COV 2.4g (casirivimab 1.2g + imdevimab 1.2g) is NO LONGER recommended** due to its lack of neutralization activity against Omicron. Other antibodies are currently being evaluated for this indication. Other mAbs should not be used as a substitute. **Colchicine and biologics (e.g., anakinra)** are **not** recommended outside of approved clinical trials.	**Therapeutic anticoagulation (LMWH preferred) may be 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-Moderately Ill Patients	See the CTC Clinical Practice Guide and Practice Tool #1: Step-by-Step Assessment for treatment recommendation for ambulatory, LTC and in-patients with mild-moderate COVID-19 with **nirmatrelvir/ritonavir, sotrovimab and remdesivir.** Recommendations regarding **colchicine, fluvoaxamine** and **inhaled corticosteroid** are also included in within these resources.		**NOT RECOMMENDED FOR ANY SEVERITY**
Discharge Patients that have recovered and are discharged from hospital	**No COVID-19 specific therapies are recommended** on discharge (includes corticosteroids and DVT chemoprohylaxis, e.g, LMWH or rivaroxaban; unless indicated for other reasons)		**Convalescent Plasma, IVIg, chloroquine** or **hydroxycholorquine, lopinavir/ritonavir, interferon IV/ SC** and **ribavirin** have been evaluated across all disease severities and have not been found to be effective against COVID-19 in clinical trials, or high-quality cliical trials are lacking. These agents are **not recommended** for prevention or treatment of COVID-19 across all disease severities.
Prophylaxis Asymptomatic patients with known COVID-19 exposure	**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 prophylaxis of COVID-19 and BC registrants must not prescribe it for this purpose. Ivermectin** should **not** be used outside of approved clinical trials.	**Bamlanivimab-etesevimab** and **REGEN-COV are not recommended** due to resistance of Omicron to these agents. Due to lack of impact on hospitalization rates or mortality and low generalizability of clinical studies, administration of any **mAbs** s **not recommended** for postexposure prophylaxis. **Tixagevimab/cilgavimab** is **NOT RECOMMENDED**, including in severely immunocompromised patients. Currently, there is a lack of high-quality evidence demonstrating a benefit of tixagevimab/ cilgavimab in preventing hospitalization from COVID-19, particularly from variants of concern (e.g., Omicron). Tixagevimab/cilgavimab was evaluated in unvaccinated non-immunocompromised individuals to prevent symptomatic infection with wild-type, Alpha and Delta virus; its role within the present vaccine and therapeutic landscape is unclear. Retrospective observational studies show it to be of minimal additive value. Tixagevimab/cilgavimab has reduced neutralization activity against BA 4/5; according to real world data, this likely leads to lower serological and clinical activity that cannot be fully overcome by a dose increase. Further, any theoretical benefit may not outweigh by the potential risk of cardiac serious adverse events (SAEs).	