Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19

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** in patients with critical COVID-19 outside of approved clinical trials as it has not demonstrated to improve survival or time to recovery. 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 AND/OR Baricitinib are 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. While head-to-head comparative data are lacking, the magnitude of benefit of each agent appears equivalent. However, more robust data exist to support the use of tocilizumab. 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 a tociluzumab or continue baricitinib. In patients who continue to deteriorate on immunomodulator monotherapy due to COVID-related inflammation/cytokine storm, the combination of **tocilizumab plus baricitinib can be considered** as the addition of baricitinib to tocilizumab has been shown to provide an incremental survival benefit of 2.4% (OR 0.79 CI 0.63 to 0.97; RECOVERY) **Tocilizumab 400 mg IV (single dose) is recommended** (REMAP-CAP, RECOVERY). Dose capping continues to be recommended over 8mg/kg due to a lack of robust drug supply and similar benefits between the two doses seen in observational studies. Tocilizumab should only be initiated when life support is required because of COVID-19 rather than other causes (such as bacterial infection, pulmonary embolism, etc). **AND/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 x 10^9/L, lymphocytes < 0.2 10^9/L, ALT or AST > 5 x ULN, or eGFR < 15 mL/min (or receiving renal replacement therapy). **Limited data exist on baricitinib in pregnancy. Risks and benefits of baricitinib should be discussed on a case by case basis with pregnant patients with critical COVID-19* **Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGEN-COV, Sotrovimab, Regdanvimab, Bebtelovimab) 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 low flow supplemental oxygen therapy	**Remdesivir is not recommended.** While remdesivir demonstrated a small survival benefit (14.6% vs. 16.3%, p=0.03) in the final analysis of SOLIDARITY, this difference was not observed when mortality was lower. Since current mortality is ~50% lower than in SOLIDARITY, the benefit of remdesivir is unlikely. Observational trials with positive results no longer show a benefit in late Omicron periods when mortality is low and patients have hybrid immunity. **Remdesivir is non-formulary** in BC hospitals due to lack of benefit in the general population with severe COVID-19. Seek expert consultation before pursuing non-formulary remdesivir for patients who are deteriorating despite optimal therapy, those with excessive risk of mortality (e.g., elderly on rituximab) or those with recurring or recalcitrant severe infection. However, the lack of evidence of benefit from remdesivir in these scenarios needs to be seriously considered. 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% (28-day mortality for tocilizumab 29% vs. usual care 33%) in patients who had CRP >75 mg/L AND on low-flow oxygen, non-invasive respiratory support, or invasive mechanical ventilation. However, considering the current low mortality, cost and supply of IL-6 blockers in Canada, CTC recommends prioritizing tocilizumab use only for critically ill patients at this time, which is the population shown to benefit most 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 who show signs of systemic inflammation/cytokine storm (e.g., C-reactive protein ≥ 50 mg/L, ferritin ≥ 1000 µg/L). Baricitinib should only be initiated when oxygen support is required due to COVID-19 pneumonia (not from other causes such as heart failure, pulmonary embolism, etc.). Baricitinib should not be administered to patients with neutrophils <1.0 10^9/L, lymphocytes <0.2 10^9/L, ALT or AST >5 x ULN, eGFR <15 mL/mmin/1.73 m²). 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, benefits vs risks of over-immunosuppression should be assessed 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*. It 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, if the risk of bleeding remains low. Pooled data from RCTs showed that therapeutic anticoagulation with LMWH/UFH significantly reduces major thrombotic events (OR 0.47; 95% CI 0.24-0.90) but may increase major bleeding (OR 1.45; 95% CI 0.77-2.70) compared with lower doses. Organ support-free days alive were significantly increased with therapeutic heparin (OR 1.29; 95% CI 1.07-1.57). Benefit is more likely in those with elevated D-dimer level or additional risk factors for thrombosis. No differences were observed in the need for invasive mechanical ventilation, intracranial hemorrhage or all-cause mortality. *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, remdesivir and sotrovimab.** Recommendations regarding **tixagevimab/cilgavimab, colchicine, fluvoxamine** and **inhaled corticosteroids** 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 chemoprophylaxis, e.g, LMWH or rivaroxaban; unless indicated for other reasons). Patients started on antivirals for mild-moderate COVID-19 in the hospital setting should finish the 3- or 5-day course of remdesivir or nirmatrelvir/ritonavir, respectively.		**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	**Nirmatrelvir/ritonavir is not recommended** for post-exposure prophylaxis. A recent RCT (EPIC-PEP) showed that a 5 or 10-day course is no better than placebo in preventing symptomactic, PCR-positive COVID-19 infection (2.6% vs. 2.4% vs. 3.9%, p=0.2). Hospitalizations were low and not statistically different (0 vs. 0 vs. 1). Due to the lack of benefit of PEP and the potential drug-drug interactions with nirmatrelvir and ritonavir, PEP should not be used in any setting, including long-term care outbreaks.	**Monoclonal antibodies 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 all Omicron variants and nearly all variants in BC are completely resistant; according to real world data, this 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).	

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