BC COVID THERAPEUTICS COMMITTEE (CTC)

Algorithm for Treatment of COVID-19 in Hospitalized Patients

DEC 2022

This flow chart can be used in therapeutic decision making for **ADULT, NON-PREGNANT** patients who are hospitalized and have a positive COVID-19 test or have symptoms consistent with COVID-19 across any disease severity. This tool includes pearls for consideration; however, as each clinical situation is unique, strong judgement is required. Expert consultation can be considered for assistance.

PCR performed?

NO	YES	
Order PCR →	Results	
	Negative	Positive

COVID-19 NOT likely. **Monitor**; if exposure occurred and pre-test probability is high, repeat PCR in 2-3 days

Assess Symptom Severity

Reflection Point: Assess symptom trajectory – patients who are improving on their own do not require treatment

Asymptomatic or minimally symptomatic

- Watchful waiting
- Assess daily for 2-3 days for symptom progression or development

Patients can shed virus for weeks after recovering from infection; treatment is not required in asymptomatic chronic shedders

Mild – Moderate
Not requiring consistent O_2 support

- 60% of patients with SARS-COV-2 in hospitals are not hospitalized DUE TO COVID-19
- Treatment is recommended for:
  - CEV 1, 2 OR 3
  - ≥70 y/o with multi-morbidity
  - ≥70 y/o with 1-2 vaccine doses and at least one chronic condition
  - ≥50 y/o with 1-2 vaccine doses and multimorbid
  - Unvaccinated who are ≥ 50 y/o OR multimorbid
  - Indigenous who are unvaccinated, ≥50 y/o with 1-2 vaccine doses OR ≥70 y/o

Nosocomial COVID and **moderate disease** (pneumonia, lower respiratory symptoms, systemic illness) are most likely to progress to severe disease; have a low threshold for treatment of symptomatic eligible patients

Is the patient eligible for treatment?

NO	YES

Severe
Requiring lo-flo supplemental O_2

Check that supplemental O_2 is required due to COVID-19 and not underlying conditions

Minimal or intermittent O_2 should be considered as moderate COVID-19, not severe

Critical
Requiring invasive and non-invasive hi-flo ventilation (flow rate > 30 L/min and FiO2 > 0.4, CPap, BiPap) or organ support

Check that ventilator or organ support is required due to COVID-19 and not underlying conditions

Start Steroid

Dexamethasone 6mg PO/IV daily x 10 days or until discharge **is recommended**

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AND

Assess for Immunomodulators

Inflammatory Markers Elevated?

Signs of COVID-19 related inflammation (CRP ≥ 50 mg/L, ferritin ≥ 1000 µg/L)?

NO	YES

Reflection Point: If inflammatory markers elevated but contraindications to baricitinib (neutrophils <1.0 x 10^9/L lymphocytes <0.2 x 10^9/L , GFR <15 mL/min, ALT or AST 5x ULN), use tocilizumab 400mg IV x 1 dose

Baricitinib
4 mg po daily (GFR ≥ 60 mL/min) or **2 mg po daily** (GFR 30-59 mL/min) or **2 mg po every 2nd day** (GFR 15-29 mL/min) up to 14 days, or until discharge **is recommended**

Tocilizumab
400mg IV x 1 dose is recommended

AND

Reflection Point: In patients deteriorating due to ongoing COVID-related inflammation despite tocilizumab, baricitinib may be cautiously considered with consultation if no contraindications (neutrophils <1.0 x 10^9/L lymphocytes <0.2 x 10^9/L , GFR <15 mL/min, ALT or AST 5x ULN)

AND

Baricitinib
4 mg po daily (GFR ≥ 60 mL/min) or **2 mg po daily** (GFR 30-59 mL/min) or **2 mg po every 2nd day** (GFR 15-29 mL/min) up to 14 days, or until discharge **may be considered**

Assess for Antivirals

Contraindications to Paxlovid?

unmanageable drug-drug interactions, GFR less than 30 mL/min, end-stage liver disease

NO	YES

Remdesivir
200mg IV x 1 then 100mg IV daily x 4 days may be considered
No renal dosing required

AND

Reflection Point: Remdesivir can be added in patients with severe COVID-19 who continue to deteriorate on baricitinib; baricitinib can be added to remdesivir if inflammatory markers become elevated

Remdesivir is NOT recommended in critical COVID

Nirmatrelvir/ritonavir (Paxlovid)
300/100mg PO BID (GFR ≥ 60 mL/min) or **150/100mg PO BID** (GFR 30-59 mL/min) **x 5 days is recommended** within 5 days of symptom onset

Remdesivir
200mg IV x 1 then 100mg IV daily x 2 days (GFR ≥ 30 mL/min) or **200mg IV x 1 then 100mg IV 48 hours later x 1 dose** (GFR < 30mL/min) **is recommended** within 7 days of symptom onset

Reflection Point: Stop Paxlovid if patient deteriorates to severe or critical COVID-19 while on treatment.

If deterioration to severe disease is seen while on remdesivir, patient can finish a 5-day course for this indication. Remdesivir should be stopped in critical COVID-19. Prolonging or re-prescribing full courses of remdesivir is not recommended.

Optimize Anticoagulation

High risk of bleeding?

age 75 or greater, GFR 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/spinal catheter

NO	YES

Therapeutic anticoagulation (LMWH preferred) **may be considered**
If used, anticoagulation for COVID-19 should start within 72 hours of admission and continue for 14 days or until hospital discharge

Prophylactic-intensity dosing of low molecular weight heparin (LMWH) for VTE prophylaxis **is recommended**

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Follow-up

Reflection Points:

Patients who were started on dexamethasone should **finish 10 days of dexamethasone** or stop at discharge, whichever is sooner

Patients who were started on remdesivir for severe COVID-19 should **finish 5 days of remdesivir** or stop at discharge, whichever is sooner

Patients who were started on baricitinib for severe disease who improve rapidly (e.g., stopped oxygen) may stop baricitinib or continue if improvement is slow

Patients who were started on therapeutic anticoagulation **should continue therapeutic anticoagulation for 14 days** or until discharge

Improvement from SEVERE to MILD-MODERATE

Progression from SEVERE to CRITICAL

Reflection Points:

Consider multi-disciplinary consultation

Patients who were started on remdesivir should **stop remdesivir**

Patients who were started on baricitinib can **continue baricitinib, continue baricitinib and receive tocilizumab x 1 dose, OR stop baricitinib and receive tocilizumab x 1 dose.** The decision depends on reason for deterioration, degree of inflammation, initial response to baricitinib and patient factors such as contraindications and gastric access

Patients who were started on therapeutic anticoagulation **should continue therapeutic anticoagulation**

Testing

- PCR testing for diagnosis of COVID-19 is indicated in all acute care settings, even if a rapid antigen test was self-administered prior to admission. See: Provincial Testing Guidelines
- As PCR is exquisitely sensitive and a positive test may indicate recovered infection or chronic shedding, symptom assessment and trajectory are paramount in guiding treatment decisions/

Corticosteroids

- Severe and Critical COVID-19:

  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.

Immunomodulators

- Severe COVID-19:

  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, RECOVERY) for patients hospitalized from COVID-19 requiring supplemental oxygen who show signs of systemic inflammation/cytokine storm (e.g., elevated 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 x 10^9/L, lymphocytes <0.2 x 10^9/L, ALT or AST >5 x ULN, GFR<15 mL/min/1.73 m^2. Patients who received immunosuppressants (high-dose corticosteroids, biologics, or JAK inhibitors) were generally excluded from RCTs of baricitinib; 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

  Tocilizumab is not recommended for patients receiving low-flow oxygen support. The RECOVERY trial found a survival benefit of 4% (28-day mortality: 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 scarcity of IL-6 blockers in Canada, CTC and CTRAWG recommend 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.

- Critical COVID-19:

  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 tocilizumab or continue baricitinib. In patients who continue to deteriorate on immunomodulator monotherapy due to COVID-19-related inflammation/cytokine storm, the combination of tocilizumab and 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 0.63-0.97; 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.).

  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 x 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

Antivirals

- Mild-Moderate COVID-19:

  Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days (150/100mg PO BID x 5 days in eGFR 30-60ml/min) **is recommended** within 5 days of symptom onset for patients at high risk of progression to severe COVID-19 (see Clinical Practice Guide for eligibility criteria) OR, if nirmatrelvir/ritonavir cannot be due to drug-drug interactions or contraindications **Remdesivir 200mg IV on day 1, followed by 100mg IV on days 2 and 3** (200mg IV on day 1, followed by 100mg IV 48-72 hours later in eGFR <30ml/min) **is recommended** within 7 days of symptom onset as an alternative to nirmatrelvir/ritonavir.

- Severe COVID-19:

  Remdesivir 200mg IV on day 1 followed by 100mg IV on days 2-5 can be considered in patients who are not receiving baricitinib for COVID-19-related inflammation/cytokine storm. Remdesivir has demonstrated a small survival (14.6% vs. 16.3%, p=0.03) in the final analysis of SOLIDARITY and need for requiring mechanical ventilation (8% vs. 15%) as a secondary endpoint of CATCO. As data supporting the use of baricitinib is stronger, baricitinib should be initiated first in those meeting criteria. Remdesivir may be added in patients who are deteriorating (but not requiring organ support), or not improving despite baricitinib as the combination has been shown to reduced recovery time and improved clinical status for patients with severe COVID-19 (ACTT-2). If remdesivir is used for this indication, a 5-day course is recommended as a 10-day course was shown to be equivalent but increased the length of hospital stay.

- Critical COVID-19:

  Remdesivir is not recommended in patients with critical COVID-19 as it has not demonstrated to improve survival or time to clinical recovery.

Anticoagulation

- Severe COVID-19:

  Therapeutic anticoagulation (LMWH preferred) can 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, 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.

- Critical COVID-19:

  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.