**Algorithm for Treatment of COVID-19 in Hospitalized Patients**

**MAY 2023**

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.

**Start Steroid**

**Assess for Antivirals**

**Assess for Immunomodulators**

**Optimize Anticoagulation**

**Follow-up**

**Contraindications to Palvulozid**

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

**Reflection Points:**

- 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.

**High risk of bleeding?**

- If used, anticoagulation for COVID-19 should start within 72 hours of admission and continue for 14 days or until hospital discharge

**Continuation of Treatment**

- Patients who were started on baricitinib and 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 co-morbidities and genetic access.

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

- Consider multidisciplinary 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, OK stop baricitinib and receive tocilizumab x 1 dose.

- Remdesivir is NOT recommended in critical COVID

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**PCR performed?**

- **NO**
  - 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

- **YES**
  - Assess Symptom Trajectory – patients who are improving on their own do not require treatment
  - Assess for Immunomodulators
  - Assess for Antivirals
  - Optimize Anticoagulation

**Mild – Moderate**

Not requiring consistent O2 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
  - Patients with TWO of:
    - ≥ 70 y/o or older (≥ 60 y/o if Indigenous)
    - Serum or urine-determined (lack of primary 2-dose mRNA series PLUS a Full booster)
    - Serious chronic medical condition such as heart failure, heart disease, stroke, diabetes, renal or liver disease, chronic lung disease, neurological conditions

**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**
    - Assess Symptom Severity
    - Severe
      - Requiring Bi-0 supplemental O2
      - Check that supplemental O2 is required due to COVID-19 and not underlying conditions
      - Minimal or intermittent O2 should be considered as moderate COVID-19, not severe
      - Check that ventilator or organ support is required due to COVID-19 and not underlying conditions
      - Clinical
        - Requiring invasive and non-invasive hi-fl0 ventilation (flow rate > 30 L/min and FiO2 >21, <84, <84, OR organ support

**Assess for Immunomodulators**

**Start Steroid**

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

**Assess for Antivirals**

**Remdesivir 200mg IV x 1 then 100mg IV daily x 4 days may be considered**

- No renal dosing required

**Reflection Points:**

- Patients who were started on baricitinib for severe COVID-19 should finish 5 days of remdesivir 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

**Follow-up**

**Improvement from SEVERE to MILD-MODERATE**

- 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

**Progression from SEVERE to CRITICAL**

**PCR performed?**

- **NO**
  - Order PCR
  - Results
    - Negative
    - Positive

- **YES**
  - Assess Symptom Trajectory – patients who are improving on their own do not require treatment
  - Assess for Immunomodulators
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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 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 m². 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.

Anticoagulation

- Severe COVID-19:

  - Baricitinib AND/OR Tocilizumab 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 requiring 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.).

Antivirals

- Mild-Moderate COVID-19:

  - Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days (150/50mg PO BID x 5 days in eGFR 30-60/mL/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 <30/mL/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 benefit (4.6% vs. 4.3%, p=0.023) 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 shown to reduce 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 mRCT). 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.