Management of suspected/confirmed COVID-19 (adults)

SARS-CoV-2 causes a self-limited influenza-like illness in the majority of cases, but can progress to severe illness with ARDS and multiorgan failure. Severe illness usually begins about 1 week after onset of symptoms and may be characterized by a progressive hypoxemic respiratory failure coupled with evidence of severe hyperimmune response.
Vaccination provides the best overall protection against severe COVID-19 disease; however older age and certain conditions are potential risk factors for severe disease even among vaccinated individuals.
Excellent supportive care remains the cornerstone of management. Eligible patients will be offered enrollment in clinical treatment trials to ensure access to best treatment options.

DEFINITIONS:

Suspected COVID-19 case: fever and/or new onset/exacerbation of respiratory symptoms and/or new onset diarrhea
Confirmed COVID-19 case: as above + lab detection of SARS-CoV-2 in respiratory sample

Recommended Admission Criteria (*use clinical judgment*)

- Respiratory criteria:
  - Dyspnea at rest or during minimal activity (sitting, talking, coughing, swallowing), *OR*
  - Respiratory rate > 22/min, *OR*
  - PaO_2 < 65 mm Hg or O_2Sat < 92%, *OR*
  - Infiltrate on CXR involving >50% of lung fields (worsening CXR if baseline abnormal)
- Non-respiratory criteria:
  - Concern re. living situation *OR*
  - Systolic BP < 100 or signs of sepsis/septic shock, *OR*
  - Altered mental status
  - Additional diagnosis requiring admission

Conditions associated with increased risk of severe COVID-19:

- Imunocompromised state: solid or hematopoietic transplant recipient, immunosuppressive therapy including high dose steroids (eg. prednisone >20mg po die for >2 weeks), HIV with CD4 < 200, primary immunodeficiency
- Active malignancy (undergoing chemo/radio/immunotherapy)
- Serious cardiovascular disease (unstable CAD, uncontrolled CHF, severe arrhythmia)
- Severe lung disease (severe asthma, COPD, CF, pulmonary fibrosis)
- Chronic kidney disease on dialysis
- Sickle cell disease
- Diabetes especially if unvaccinated
- Pregnancy especially if unvaccinated
- Obesity (BMI 35)
- Down Syndrome (trisomy 21)
- Age > 65y especially if unvaccinated

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PHARMACOLOGIC MANAGEMENT

OUTPATIENT (no criteria for admission, mild disease) *Offer enrolment in clinical trial and contribution to COVID biobank; call ext. 32033 or email COVID.Research@muhc.mcgill.ca*	
MILD disease **(O_2 Sat > 92%, no supplemental O_2)**	If high-risk of progression to severe disease* (see box above) *AND* <7 days since onset of symptoms: • Instructions for self-quarantine at home (as per Public Health guidelines) AND • Acetaminophen 650 mg po q4-6h PRN (*avoid if severe hepatic impairment)* AND • Apply decision tree to assess if candidate for **early antiviral therapy** [1,2,6] If NOT high-risk for progression to severe disease* (see box above) OR >7 days since onset of symptoms: • Instructions for self-quarantine at home (as per Public Health guidelines) AND • Acetaminophen 650 mg po q4-6h PRN (*avoid if severe hepatic impairment) AND* • *Consider* budesonide 800 mcg inh BID x 14 days if cough/shortness of breath
HOSPITALIZED PATIENT (*Ct values of SARS-CoV2 PCR testing should NOT be used to guide treatment decisions*) *Follow Admission guide for COVID-19 (and IPC guidelines for isolation)* *Call coordinator for COVID-19 treatment trials (ext. 32033) or email COVID.Research@muhc.mcgill.ca*	
MILD disease **(O_2 Sat > 92% on no supplemental O_2)**	• Acetaminophen 650 mg po q4-6h PRN (*avoid if severe hepatic impairment*) *AND* • **Dalteparin**[3,4] 200 U/kg S/C die (max dose 20,000U die) **IF** expected hospitalization > 3 days *AND* D-dimer positive (until clinical improvement *or* 14 days, whichever comes first) *AND* If high-risk of progression to severe disease*, apply decision tree for antiviral therapy
MODERATE disease **(Supplemental low-flow O_2 for O_2Sat > 92%)**	• Acetaminophen 650 mg po q4-6h PRN (*avoid if severe hepatic impairment*) *AND* • **Dalteparin**[3,4] 200 U/kg S/C die (max dose 20,000 U) (until clinical improvement *or* x 14 days, whichever comes first) *AND* • **Dexamethasone**[5] 6 mg po daily x 10 days (or until discharge, whichever comes first; IV only if cannot tolerate po) *AND* • **Remdesivir**[6] 200 mg IV x 1 then 100 mg IV q24h x **4 days**
SEVERE disease **(on High-flow nasal cannula, invasive or non-invasive mechanical ventilation to maintain O_2 Sat > 92%)**	**CONSULT ID** • Acetaminophen 650 mg po q4-6h PRN (*avoid if severe hepatic impairment*) *AND* • **Dalteparin** 5000 units S/C daily *AND* • **Dexamethasone**[5] 6 mg po/IV daily x 10 days *AND* • **Empiric antibiotics**[7] **(reassess after 48 hours, maximum duration 7 days)** - **Ceftriaxone** 2 g IV q24h If < 5 days since admission - **Piperacillin-tazobactam**[8] 4.5 g IV q8h (extended infusion over 3h) if ≥ 5 days since admission or severe immunocompromise **IF** patient **< 24h** since meeting severity criteria **AND** bacterial superinfection excluded **AND** CRP >75 mg/mL: • **Tocilizumab**[9] 400mg IVx1 if weight <75kg (if weight 75-100kg: 600mg IVx1; if >100kg: 800mg IVx1) *OR* **Baricitinib**[10] 4 mg po die x 14 days

ADDITIONAL CONSIDERATIONS

Early pre-emptive therapy options include Sotrovimab[1], Nirmatrelvir/ritonavir[2], Remdesivir[6]

[1]Sotrovimab: monoclonal antibodies neutralizing Spike protein of SARS-CoV2.

- **Not effective vs Omicron BA2 variant** currently predominant in Quebec
- No benefit and possible harm in severe disease [except if *known* seronegative for SARS-CoV2]
- COVID-19 vaccination should not be given for at least 1 month after administration.
- May cause rash/allergic reaction. Monitor for adverse reaction for 1 hour after infusion.

[2]Nirmatrelvir/ritonavir (Paxlovid): inhibits SARS-CoV2 viral replication via binding of a viral protease

- Dosage ajustement required if eGFR between 30 and 60 mL/minute; to be avoided if <30ml/min
- Decreased progression to hospitalization when given early (<5d) after infection, in high-risk non-vaccinated individuals; No benefit in hospitalized/severe disease; unclear benefit in appropriately vaccinated individuals
- **Many drug-drug interactions** (with inhibitors or inducers of CYP3A4, and with substrates of CYP3A4, CYP2D6, p-glycoprotein, BCRP and OATP1B1/1B3 for up to 5 days after the end of Paxlovid), particularly with transplant recipients on calcineurin inhibitors; Pharmacy consultation strongly recommended.

[3] Dalteparin:

- Therapeutic anticoagulation (TAC) superior to prophylactic anticoagulation for mild and moderate disease particularly if **D-dimer positive (if D-dimer level > age/100 or >0.5, whichever is higher**)
- In pregnancy: Consider 100 U/kg S/C BID dosing for more flexibility around timing of delivery
- Obesity: use actual body weight but maximum dose 20,000U s/c die
- Renal adjustement: for eGFR 20-30 mL/min --> 100 U/kg S/C BID. Patients with eGFR <20 mL/min were not well represented in the clinical trials, would not use LMWH. Also unclear if benefits of anticoagulation outweigh risks in this population. If decision to anticoagulate, consider unfractionated heparin (UFH): bolus 80 U/kg then 18 U/kg/h - follow MUHC PPO for monitoring and dose adjustement

[4] Contra-indications to TAC:

- GI bleed in last 3 months; recent major surgery (< 14 days); bleeding disorder (e.g. hemophilia); Thrombolysis within previous 7 days; other physician-perceived contra-indication to anticoagulation
- Brain tumor, brain metastases (unless recent imaging shows no bleed); cerebral aneurysm or intracerebral arteriovenous malformation; history of intracranial bleeding; presence of an epidural or spinal catheter

[5] Dexamethasone:

- Monitor glycemia (CBGM) and adjust control (following MUHC PPO)
- For patients on steroids for another indication: if high dose, continue same steroid formulation; if low dose, switch to dexamethasone 6 mg po/IV die; can replace with Hydrocortisone 50 mg IV q8h
- If pregnancy and possibility of pre-term deliverly: give dexa 6mg po Bid x 4 doses then complete 10 day course with methylprednisolone 32mg po/Iv die

[6] Remdesivir:

- Decreases risk of hospitalization by 87% in unvaccinated outpatients ≥ 60y old or with ≥1 risk factor for progression to severe COVID-19. Efficacy unclear in vaccinated patients;
- Some benefit in terms of mortality and time to recovery in moderate disease;
- Highest benefits expected in early stages when virus actively replicating (<10d of symptoms).
- Potential adverse events: liver and renal (monitor LFTs and creat daily)
- No renal adjustement recommended based on review of most recent evidence

[7] Empiric antibiotics: not recommended for mild-moderate disease (very low risk of bacterial infection)

- **Severe disease: secondary bacterial infections occur in about 15%.** Collect blood and sputum samples before starting antibiotics and reassess choice of antibiotics within 48 h.

[8]If type I hypersensitivity to penicillin: replace with meropenem 1 g IV q8h

[9]Tocilizumab: is an anti-IL6 receptor antibody - in limited supply (global shortages):

- **Risk of serious bacterial infection** (avoid if known bacterial superinfection/sepsis; consider measuring Procalcitonin level if uncertain); risk of allergic reaction, liver failure; caution if LFTs >1.5x ULN at baseline

[10]Baricitinib: Renal dose adjustment if eGFR 30-60: 2mg po die; if eGFR 15-30: 1mg po die; if eGFR <30: not recommended

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