Last updated: December 22, 2021 – all information subject to change.
See AHS Insite COVID-19 resources for current version.

Current Guidance for the Management of Adult Hospitalized Patients with COVID-19

Prepared By: The COVID-19 Therapeutics Working Group, Alberta Health Services

Note: This document represents updated guidance (previous update December 14, 2021) and will be updated as relevant new information becomes available. As such, the most current web-based version of this document should preferentially be used.

The COVID-19 Therapeutics Working Group has updated the evolving evidence base for this document as best as possible but recognizes that future updates will be required based on ongoing therapeutic trials and emerging evidence. Supportive care remains an important component of therapy for individuals infected with SARS-CoV-2. Updated COVID-19 management guidelines from the Public Health Agency of Canada (PHAC), Association of Medical Microbiology and Infectious Diseases (AMMI), Canada/Canadian Critical Care Society (August 21, 2020)[1], the Infectious Diseases Society of America (IDSA) (September 3, 2021)[2] and the Alberta Health Services COVID-19 Scientific Advisory Group[3] have been reviewed in preparing this update. Full details are available in the hyperlinks above and the referenced documents below.

Consultation with other specialties (e.g. Infectious Diseases, Respiratory Medicine, Critical Care, General Internal Medicine) who are most likely to be familiar with the rapidly evolving literature can be considered to help assess the risks and benefits for an individual patient. As recommended by AHS Ethics, any off-label use of medication requires the prescriber's careful consideration of risk/benefit, consultation between experts and attending physician as needed, and documenting consent from the patient or caregiver after discussion of the current state of evidence of benefit and harms. Adverse events with respect to off-label use of medications for inpatient treatment should be documented and reported by clinicians through the AHS Reporting and Learning System for Patient Safety.

The guidance provided in this document does not replace best clinical judgment and/or expert consultation but rather is meant to inform clinicians of the most current management guidelines to facilitate best use of therapeutic options for patients with COVID-19.

Guiding Principles

1) The use of antiviral or other immunomodulatory treatments, other than those recommended below, for patients with COVID-19 should occur within the context of controlled clinical trials wherever possible, given the currently available limited therapeutic options for which evidence-based data are available.

2) If the use of antiviral or immunomodulatory agents for COVID-19 outside of clinical trials is being considered, the potential risks (adverse reactions, drug interactions (see COVID drug interactions or Lexicomp) versus unverified benefits must be considered and discussed with the patient or caregiver, and consent documented on the chart.

3) Bacterial co-infection in patients with early COVID-19 is uncommon. Do NOT routinely add antibacterials unless bacterial infection is strongly suspected. If indicated, antibacterials should be reassessed within the first 3 days after initiation to determine if continuation is necessary, or to de-escalate and/or optimize therapy in accordance with the principles of stewardship to avoid short-term adverse-effects and negative long-term consequences of increased microbial resistance.

Current Practice Guidance

1. General Considerations

- Patients with mild suspected or confirmed COVID-19 should not require hospitalization, unless there is a clinical concern for rapid deterioration, significant underlying co-morbidities, extenuating sociodemographic circumstances, or an inability to return promptly to hospital. Patients with mild COVID-19 and their caregivers should be provided with information on symptom management and informed of the signs and symptoms of complications that should prompt medical re-evaluation.
- Patients with moderate suspected or confirmed COVID-19 (i.e. with clinical signs of pneumonia, SpO2 ≥ 90% on room air, but no signs of severe pneumonia) who are not determined to be at high risk of deterioration may not require hospitalization, but they should self-monitor and be counseled along with their caregivers about the signs and symptoms of complications that should prompt medical re-evaluation.
- Patients with severe suspected or confirmed COVID-19 and respiratory distress, hypoxemia, or shock should receive supplemental oxygen therapy immediately with target saturations of > 94% SpO2 during resuscitation. Patients with severe illness should be closely monitored for signs of clinical deterioration, specifically rapidly progressive respiratory failure, or shock.
- In hospitalized adult patients who meet criteria for severe disease (defined by the IDSA as SpO2 <94% on room air), and requiring supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation, clinicians should prescribe dexamethasone 6 mg IV/PO daily for 10 days (or equivalent glucocorticoid dose)[4], or until off oxygen or discharged, whichever is earlier. Glucocorticoids are not recommended in patients who do not have hypoxemia requiring supplemental oxygen.

2. Antibacterials

- For those patients with suspected or confirmed mild to moderate COVID-19, antibiotics should **not** be routinely prescribed unless there is clinical suspicion of a bacterial infection.
- For patients with severe COVID-19 but not critically ill, do NOT routinely add antibacterials unless bacterial infection is strongly suspected.
- For critically ill patients with suspected or confirmed severe COVID-19, empiric antibacterial agents to treat all likely pathogens causing severe acute respiratory bacterial infection and sepsis as soon as possible are reasonable, and optimally should be initiated within 1 hour of initial patient assessment for patients with sepsis.
- If indicated, empiric antibiotic treatment should be based on the working clinical diagnosis (e.g., community-acquired pneumonia, health care-associated pneumonia or sepsis), local epidemiology, and susceptibility data. See references such as Bugs & Drugs for empiric antibacterials.
- Use of antibacterial therapy should be judicious with reassessment after 3 days for de-escalation and/or optimization of therapy, in accordance with the principles of stewardship, after review of the clinical status, laboratory and imaging findings, and microbiology results.

3. Antivirals/Immunomodulators

- Remdesivir is approved for use in adult hospitalized patients with COVID-19 pneumonia if they are not mechanically ventilated[5]. Patients can be given remdesivir if they are acutely ill from COVID-19, or if they are immunocompromised according to the definition in the AHS Infection Prevention and Control Management of Severely Immunocompromised COVID-19 Patients document.
- Tocilizumab is approved for use in patients with severe COVID-19 pneumonia[6]. To be eligible, patients must have been admitted to hospital for COVID-19 pneumonia 7 or fewer days ago, or have developed symptoms from hospital-acquired COVID-19 pneumonia 7 or fewer days ago. They must also be experiencing significant progressive respiratory failure due to COVID-19 pneumonia that requires they receive ventilation (invasive or non-invasive) or supplemental oxygen to achieve a minimum SpO_2 of 90%. Supplemental oxygen is defined as heated high flow oxygen with $FiO_2 \geq 0.5$, nasal prong delivered oxygen at a rate of 6 L/minute, or mask delivered oxygen with $FiO_2 \geq 0.5$. Furthermore, tocilizumab must be initiated within 24 hours of initiation of mechanical ventilation or, if not mechanically ventilated, as soon as possible. Tocilizumab is restricted for this indication to one dose per patient per hospitalization, dosed as follows:

≤ 40 kg:	8 mg/kg
> 40 kg:	400 mg

  Tocilizumab should not be used in patients who have received baricitinib for the treatment of COVID-19 during their current hospitalization. They each work on the same inflammatory pathway, so added benefit is unlikely. Due to their immunosuppressant effects, combination therapy may have adverse effects.[7]

- Baricitinib is approved for use in patients with severe COVID-19 pneumonia. To be eligible patients must be experiencing significant progressive respiratory failure due to COVID-19 pneumonia that requires they receive ventilation (invasive or non-invasive) or supplemental oxygen to achieve a minimum SpO_2 of 90%. Supplemental oxygen is defined as heated high flow oxygen with $FiO_2 \geq 0.5$, nasal prong delivered oxygen at a rate of 6 L/minute, or mask delivered oxygen with $FiO_2 \geq 0.5$. Baricitinib is an oral tablet given by mouth or enteral tube 4 mg once daily for 14 days or until discharge, whichever is sooner. The main trial[8] upon which approval of use was based excluded patients with eGFR < 30 mL/min/1.73m^2. It was dosed at 2 mg daily for those with eGFR 30 to < 60 mL/min/1.73m^2. However, the US Food and Drug Administration Emergency Use Authorization (FDA EUA)[9] also lists dosing of 1 mg for patients with eGFR 15 to < 30 mL/min/1.73m^2. Baricitinib 1 mg tablets are not available in Canada, so for patients with eGFR in this range, the recommended dose is 2 mg every other day. Baricitinib should not be used in patients who have received tocilizumab for the treatment of COVID-19 during their current hospitalization. They each work on the same inflammatory pathway, so added benefit is unlikely and due to their immunosuppressant effects, combination therapy may have adverse effects.[7]

- Casirivimab/imdevimab
  Of note, casirivimab-imdevimab fails to neutralize the Omicron variant in *in vitro* assays[11,12]. If it is confirmed or suspected that a patient is infected with the Omicron variant, casirivimab-imdevimab should not be used. In the future, if Omicron prevalence in hospital increases, it may be necessary to confirm presence of the Delta variant before considering treatment with casirivimab-imdevimab.

  Casirivimab/imdevimab is approved for use in patients hospitalized due to laboratory-confirmed COVID-19 if they weigh at least 40 kg and are aged 12 or older. Patients are eligible for treatment in one of two ways[10]:

  (1) if patients have no documented history of COVID-19 infection, have not previously received treatment with a COVID-19 neutralizing antibody (except bamlanivimab monotherapy), and have not received any doses of a COVID-19 vaccine (unless fewer than 14 days have elapsed since receiving their first dose), they must also then test negative on a COVID-19 lab-based or rapid serology test OR,
  (2) if patients are severely immunocompromised, they are eligible for treatment without requiring serology testing, even if they have a history of vaccination or COVID infection. The definition of severely immunocompromised is taken from the AHS Infection Prevention and Control Management of Severely Immunocompromised COVID-19 Patients document.

  Of note, the dosage of casirivimab/imdevimab for inpatients is 4 g/4 g. This can be obtained using 3 kits of the commercially available product, which yield 33.3 mL (3996 mg) of each ingredient, which rounds to 4 g.

  Casirivimab/imdevimab is not currently approved for outpatient use in AHS.

- Sotrovimab is approved for use in Alberta for adults with mild to moderate COVID-19 symptoms who have a positive PCR test and are able to receive treatment within 5 days of symptom onset[13] and meet ONE of the following THREE criteria:
    1. Outpatients, or inpatients admitted for non-COVID reasons, who are unvaccinated
       AND
       have AT LEAST ONE of the following:
        - Age 55 and over, regardless of comorbidities,
        - Age 18 and over with at least one of the following comorbidities:
            - Diabetes requiring medication
            - Obesity (BMI > 30 kg/m^2)
            - Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2)
            - Congestive heart failure (New York Heart Association class II, III, or IV)
            - Chronic obstructive pulmonary disease
            - Moderate-to-severe asthma
        - Pregnancy
    2. Outpatients, or inpatients admitted for non-COVID reasons, regardless of vaccination status who are immunocompromised, defined as:
        - Transplant patients (solid organ or stem cell)
        - Oncology patients who have received a dose of any IV or oral chemotherapy or other immunosuppressive treatment since December 2020
        - Patients with inflammatory conditions (e.g. rheumatoid arthritis, lupus, inflammatory bowel disease) receiving a dose of any systemic immunosuppressant since December 2020.
    3. Hospital-acquired COVID-19 in patients admitted for non-COVID reasons, regardless of vaccination status

  Sotrovimab appears to maintain neutralizing activity against the Omicron variant, albeit at reduced levels compared to the Delta variant[11,12]. There is currently no clinical evidence to support the use of sotrovimab in patients hospitalized due to COVID-19. The ACTIV-3-TICO trial randomized 344 inpatients to receive either sotrovimab (n=169) or placebo (n=175). The trial was stopped early due to futility, meaning the evidence to date suggested it was of no benefit. Among sotrovimab recipients, there was one case of anaphylaxis and one case of cytokine release syndrome[14]. Therefore sotrovimab is not recommended as a replacement for casirivimab-imdevimab in patients hospitalized due to COVID-19.

- Bamlanivimab is no longer available within AHS. All available stock expired. No future purchases will be made due to greater than 10-fold reduction in neutralizing activity against variants of concern[15], particularly Delta and Omicron variants, which are the dominant variants in Alberta as of December 22, 2021.

- Consideration of all other investigational antivirals or immunomodulators (e.g. lopinavir/ritonavir, famotidine, and colchicine) should be only under ethics approved, controlled trials.

- Awaiting more clinical trial data, fluvoxamine is not recommended for routine use as outpatient therapy of COVID-19, outside of approved clinical trials.
- The use of hydroxychloroquine, or any hydroxychloroquine combinations (e.g. hydroxychloroquine plus azithromycin), is not recommended as a treatment in patients with COVID-19.
- Ivermectin should not be used for the prevention or treatment of COVID-19.[16] Its use is not supported by evidence[17].
- Convalescent plasma is not recommended as a treatment in patients with COVID-19. Evidence suggests it has no benefit[18].

4. General Investigations

Please note the listed investigations below are for clinical consideration and not required tests. Please use the laboratory tests and Investigations incorporated into care pathways and order sets if there are differences between those and the list below.

4.1. General Laboratory tests:

Laboratory tests may not be required in otherwise ambulatory patients who are clinically stable, and not felt to be at elevated risk of decompensation. In the presence of higher clinical severity and/or comorbidities, the following laboratory tests may be considered:

- CBC & differential - *low lymphocyte count and/or neutrophil/lymphocyte ratio of >3.13 may be suggestive of COVID-19/more severe disease*
- AST, ALT, bilirubin, Cr, CRP, Urea
- D-dimer, INR
- Blood cultures
- COVID-19 PCR and RPP swabs OR sputum or ET aspirate or bronchoscopic samples for COVID-19 PCR

Also consider for select patients:

- HIVAb
- MRSA nasal swab (to determine need for empiric MRSA pneumonia coverage pending cultures)

4.2. CXR - AP (portable) or PA/LAT depending on site policies for ED based COVID-19 patients

4.3. Laboratory tests that can be considered in specific patients based on clinical status and comorbidities (NB: the current literature does not support a specific role for these parameters in guiding clinical management but they may be useful in evolving prognostic models):

- ABG
- fibrinogen
- ferritin
- troponin
- If immunocompromised and clinically indicated, ET aspirate, bronchoscopy (if required), or induced sputum for PJP and/or mycobacterial and /or fungal assessment

5. Other considerations

- Clinical progression to more severe disease usually begins between 5-7 days after symptom onset. Risk factors for disease progression include older age and presence of underlying medical conditions (e.g. hypertension, obesity, diabetes, chronic lung diseases, and immunocompromised state). However, younger, previously healthy individuals can develop severe illness
- If oxygen demand is increasing, consider early referral for appropriate respiratory supports depending on access and infrastructure.
- There is no evidence that ACE Inhibitors and Angiotensin Receptor Blockers need to be stopped. There is a theoretical concern about ACE inhibition and viral receptors but there are no clinical data supporting risk. Major cardiovascular societies (Hypertension Canada Statement on COVID-19 ACEi/ARB) recommend that suspected and confirmed COVID-19 patients on ACE inhibition should be maintained on their therapy if it is otherwise indicated to avoid decompensation of cardiac disease.
- There is no specific contraindication to NSAIDS: AHS SAG Use of NSAIDs Review . As other symptomatic therapy can be substituted (acetaminophen, appropriately dosed) it may be reasonable to prefer acetaminophen to NSAIDS for COVID-19 symptoms, but patients with inflammatory conditions on stable doses of NSAIDS should remain on them.

Submitted by Dr. John Conly, Dr. Lynora Saxinger, Susan Fryters, Tony Nickonchuk, and Jeremy Slobodan on behalf of the COVID-19 Therapeutics Working Group and reviewers (Critical Care, Infectious Diseases, Pharmacy, Emergency Medicine, Pulmonary Medicine, Immunology). Reviews of this document were also done by members of the Divisions of Infectious Diseases in the Departments of Medicine at the University of Calgary and the University of Alberta.

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