

## Recommendations for Antimicrobial Management of Adult Hospitalized Patients with COVID-19

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*Note: This is interim guidance and this document will be frequently updated as new information becomes available. As such, the most current web-based version of this document should preferentially be used.*

The COVID-19 Antimicrobial Management Working Group notes that there are no fully evidence-based effective therapies for the treatment of the novel coronavirus, SARS-CoV-2, and **supportive care remains the mainstay of therapy for infected individuals**. Prophylaxis, preemptive therapy are outside the scope of this document. Updated COVID-19 therapy guidelines from the [Public Health Agency of Canada \(PHAC\)/Association of Medical Microbiology and Infectious Diseases \(AMMI\) Canada](#), [the Infectious Diseases Society of America \(IDSA\)](#), [the American Thoracic Society \(ATS\)](#), and the [AHS ECC Scientific Advisory Group review of hydroxychloroquine](#) evidence have been reviewed in preparing this update.

### **Recommendations:**

- 1) The use of experimental treatments for patients with COVID-19 should occur within the context of controlled clinical trials**
- 2) There should be no COVID-19-specific therapies in order sets or standing orders**  
*Rationale: To date, there is no proven specific therapy for COVID-19. Experimental treatments cannot be routinely recommended given equivocal data on benefit and emerging data on harm.*
- 3) If, after review of these recommendations and the guidelines mentioned above, the use of agents for COVID-19 outside of clinical trials is being considered, the significant potential risks** (adverse reactions, including QT interval prolongation (see [QTc-prolonging medications](#)); drug interactions (see <http://covid19-druginteractions.org/> or Lexicomp)) **versus unverified benefits must be considered and discussed with the patient, and consent documented on the chart.**

Consultation with other specialties (e.g. Infectious Diseases, Respiratory Medicine) 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 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 at <https://insite.albertahealthservices.ca/tools/rls/Page1820.aspx>.

## **Considerations for Potential COVID-19 Antiviral Agents**

**Consult your site administration or Pharmacy department to determine if enrollment into clinical trials is possible.**

- Clinicians may be interested in pursuing any available therapy. A rapid review of antiviral therapies requested by the Public Health Agency of Canada (February 26, 2020) concluded “The current evidence for the effectiveness of antiviral therapies for coronavirus is not conclusive and suffers from a lack of well-designed prospective trials or observational studies. None of the interventions examined in this review can be recommended for use in patients with coronavirus”. Three major therapy guidelines ([PHAC/AMMI Canada](#), [IDSA](#), [ATS](#)) released in the last week support this assessment. Please also refer to the [Scientific Advisory Group Rapid Review](#) on hydroxychloroquine for more information about that agent.
- The three agents that are currently felt to offer the best ratio of possible benefit to harm (and are being assessed for further study in the CATCO trial) are:
  - i. lopinavir/ritonavir (Kaletra)
  - ii. hydroxychloroquine (Plaquenil)
  - iii. remdesivir (pending availability)

## **Considerations for Antibiotic Therapy (see below)**

- Antibiotics will have a limited role in managing COVID-19 patients, but recognizing the frequency with which antibiotics are used in patients with acute undiagnosed pneumonia syndromes and Acute Respiratory Distress Syndrome (ARDS), as well as the role of guidance and stewardship, the recommendations provided here are for:
  - i. empiric management of patients with severe pneumonia while COVID-19 is being confirmed and bacterial infection excluded, and
  - ii. initial management of potential bacterial superinfection.

*Please note the listed investigations below are for clinical consideration and not required tests. Work is underway to standardize the laboratory tests and investigations in standing orders and care pathways. Please use the Laboratory tests and Investigations incorporated into care pathways and order sets if there are differences between those and the list below.*

## **Investigations for suspect or confirmed COVID-19 patients under consideration for admission, or being admitted:**

### 1. 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
- Blood cultures
- COVID-19 PCR and RVP swabs OR sputum or ET aspirate for COVID-19 PCR

Also consider for select patients:

- HIVAb
  - Sputum (or endotracheal (ET) aspirate if intubated) for Gram stain and culture. NB: Do not do bronchoscopy only to procure specimens.
  - MRSA nasal swab (to determine need for empiric MRSA pneumonia coverage pending cultures)
2. CXR - AP (portable) or PA/LAT depending on site policies for ED based COVID-19 patients
  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
    - INR
    - D-dimer
    - fibrinogen
    - ferritin
    - troponin
    - If immunocompromised and clinically indicated, ET aspirate, bronchoscopy (if required), or induced sputum for PJP

### **Other considerations for Patients Hospitalized with COVID-19**

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.

- **Avoid** nebulized medications and do not do bronchoscopy for obtaining specimens alone (ET aspirate preferred) to reduce aerosolization risk
- If oxygen demand is increasing, **consider early referral for appropriate respiratory supports depending on access and infrastructure**, as patient outcomes may be superior and planned intubations are at a lower risk for infection transmission than emergent ones.
- **There is no evidence that ACE Inhibitors and Angiotensin Receptor Blockers need to be stopped.** There is a theoretic concern about ACE inhibition and viral receptors there are no clinical data supporting risk. Major cardiovascular societies (<https://hypertension.ca/wp-content/uploads/2020/03/2020-30-15-Hypertension-Canada-Statement-on-COVID-19-ACEi-ARB.pdf>) recommend that suspect 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:** There is current anecdotal concern about the antecedent use of NSAIDs in patients with severe disease, but no

clinical data are yet available. 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.

Other investigational therapies that are **NOT** currently recommended:

- High dose steroid therapy – may cause harm; worse outcomes in SARS and influenza
- IVIG – IS not expected to have neutralizing antibody, and may worsen ARDS
- Ribavirin as an adjunct to lopinavir/ritonavir - high dose has toxicity concerns, and must be used in combination
- Anti-IL6 inhibitors (tocilizumab) and other immune modulating therapies for CRS (anakinra, other) – At this time in AHS, immune modulating therapies for COVID-19 can only be pursued in the context of clinical trials. If a clinician would like AHS to provide immunomodulatory therapy, an application must be made through STEDT, and it will be considered based on the evidence submitted.

### **Empiric Antimicrobial Therapy of Pneumonia in Hospitalized Suspect COVID-19 ADULT Patients**

For patients who are pending confirmation of COVID-19 infection, with possible bacterial infection, the following initial therapy can be considered (and may be stopped if COVID-19 is confirmed as the cause of pneumonia)

*For antimicrobial recommendations in other settings (e.g. outpatient, long term care) or circumstances (bronchiectasis, allergies), refer to other references such as [Bugs & Drugs](#).*

**\*\*REASSESS at 48-72 hours WITH VIRAL AND BACTERIAL LAB RESULTS\*\***

[Ceftriaxone 1 g (2 g if > 100 kg) IV daily x 3 days

**AND** one of:

Azithromycin 500 mg PO (IV if NPO) daily x 3 days

**OR**

Doxycycline 200 mg PO then 100 mg PO BID x 3 days]

*Alternative:* levofloxacin 750 mg PO (IV if NPO) daily

*If history of MRSA colonization or high suspicion for MRSA, add:*

Vancomycin 25-30 mg/kg IV load (round to nearest 250mg; max 3 g) followed by 15 mg/kg (round to nearest 250mg; max 2 g) q 8-12h for target trough 15-20 mg/L x 3 days

*Alternative* if renal dysfunction or known prior MRSA pneumonia: Linezolid 600 mg IV/PO q 12h x 3 days

Discontinue vancomycin or linezolid if MRSA screening swab negative OR if bacterial respiratory cultures are negative for MRSA

*If symptoms clinically compatible with influenza and influenza RVP pending or positive, consider:*

Osetamivir 75 mg PO bid (if normal renal function), discontinue if influenza RVP negative.

### **Management of Possible Secondary Bacterial Infection/Ventilator Associated Pneumonia in Adult COVID-19 patients**

See other references for HAP/VAP such as [Bugs & Drugs](#).

Culture directed therapy is preferred; the following are empiric therapy recommendations pending sputum/ET aspirate culture results:

**\*\*REASSESS at 48-72 hours WITH BACTERIAL LAB RESULTS\*\***

Piperacillin-tazobactam 4.5 g IV q6h x 3 days

**OR**

Meropenem 500 mg IV q6h x 3 days

**Plus**, if not documented MRSA negative, vancomycin or linezolid as listed above

Discontinue vancomycin or linezolid if MRSA screening swab and bacterial respiratory cultures are negative for MRSA.

*Worsening pneumonia may also be due to inflammation so prolonged antibiotic therapy beyond 3- 5 days in the absence of positive cultures is not recommended.*

## Selected references:

1. [American Thoracic Society](#) COVID-19: Interim Guidance on Management Pending Empirical Evidence.
2. Arabi YM, et al. Am J Respir Crit Care Med. 2018;197(6):757-767.
3. Arabi YM, et al. Clin Infect Dis. 2019 Jun 25. pii: ciz544.
4. Chu CM, et al. Thorax. 2004;59(3):252-6.
5. Cortegiani A, et al. J Crit Care 2020.
6. Gilead Sciences. January, 2020 (web link)
7. [Infectious Diseases Society of America \(IDSA\)](#) Guidelines on the Treatment and Management of Patients with COVID-19
8. Lee N, et al. N Engl J Med. 2003;348(20):1986-94.
9. Lee N, et al. J Clin Virol. 2004;31(4):304- 9.
10. Loutfy MR, et al. JAMA. 2003;290(24):3222-8. Cao B, et al. NEJM Mar 18.
11. Mulangu S, et al. N Engl J Med. 2019;381(24):2293-2303.
12. Park SY, et al. J Hosp Infect. 2019;101(1):42-46.
13. Paton NI, et al. Lancet Infect Dis. 2011;11(9):677-83.
14. [Public Health Agency of Canada \(PHAC\)/Association of Medical Microbiology and Infectious Diseases \(AMMI\) Canada](#) Clinical management of patients with moderate to severe COVID-19 - Interim guidance
15. Sheahan TP, et al. Nat Commun. 2020;11(1):222.
16. Stockman LJ, et al. PLoS Med. 2006;3(9):e343.
17. Sung JJ, et al. Thorax. 2004;59(5):414-20.
18. Yao X, et al. Clin Infect Dis. 2020 Mar 9, ciaa237.
19. Zumla A, et al. Lancet. 2015;386(9997):995-1007.

Additional resource: bibliography and review can be found at

<https://pubs.acs.org/doi/10.1021/acscentsci.0c00272>

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