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

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

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 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, and pre hospital therapy are outside the scope of this document. This recommendation document is not a universal endorsement of these agents, but is meant to support case-by-case basis decision making.

1. Considerations for Potential COVID-19 Antiviral agents

- Clinicians may be keen to pursue 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”.

- Current literature (to March 20, 2020 including preprints) has been reviewed for the purpose of this document. Several antiviral agents under evaluation are not available to the Alberta population for the foreseeable future, and, thus, the two agents that are currently felt to offer the best ratio of possible benefit to harm are lopinavir/ritonavir (Kaletra) in early (<12 days) infection, and hydroxychloroquine (Plaquenil) (not timing restricted (see below for details).

- Given the potential activity of the investigational agent remdesivir (which has NOT been approved by Health Canada), the working group recommends Infectious Diseases (ID) consultation (in person or by phone) to facilitate:
  
  a) Compassionate access requests to Gilead Sciences*; OR

  b) Special Access Program (SAP) application for severe COVID-19 cases.

Other possible treatments should not be deferred awaiting availability of remdesivir.

*Please note that as of March 22, 2020, Gilead is transitioning from individual compassionate use requests for remdesivir to expanded access programs, details of which are forthcoming. In the interim, remdesivir compassionate use requests have been restricted to pregnant women and children under 18 years with confirmed COVID-19 and severe manifestations of disease.
2. Considerations for Antibiotic Therapy

- Antibiotics will have a limited role in managing COVID-19 patients, but recognizing the frequency with which antibiotics are used in patients with 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.

3. Immune Modulating Therapies

- As ARDS and cytokine release syndrome (CRS) are important manifestations of severe disease, there is interest in pursuing use of various immune modulating therapies. However, choice of agent, sustainability, and risk benefit ratio are controversial and lack clinical data. Evidence review for immunomodulators is ongoing and use is not currently recommended. Clinical trials or compassionate use protocols in development can be ascertained through Infectious Diseases consult (site based or by telephone consultation).
CRITERIA TO CONSIDER INVESTIGATIONAL ANTIVIRAL THERAPY in Hospitalized Adults*
(*Management of Ambulatory Patients will be addressed in a separate recommendation document)

Laboratory-confirmed COVID-19 infection requiring hospitalization for management of pneumonia

Patients with highest risk of COVID-19 related adverse outcomes should be particularly considered for treatment with off-label antiviral drugs:

   - Age > 60 years
   - Age > 50 years plus one of
     - hypertension, diabetes, structural lung disease (e.g. COPD), or high or intermediate risk immunocompromised (see appendix)
   - Other adult patients with severe disease (ARDS, respiratory failure, multi-organ failure)

Suggested Investigations prior to considering investigational therapies for COVID-19 patients:

1. Routine labs (CBC & differential, AST, ALT, bilirubin, Cr, CRP, blood cultures); HIVAb, HBsAg, HCV Ab; lipase, pregnancy test

2. Specific investigations:
   - D-dimer; troponin; LDH (secondary infection and prognostic indicators)
   - CXR and/or CT chest
   - ABG (selected patients)
   - ECG (baseline and monitoring for QTc prolongation if on QT prolonging agents)
   - COVID-19 PCR testing and RVP (Nasopharyngeal swab) (repeat weekly)
   - Sputum or endotracheal aspirate if intubated (avoid bronchoscopy simply for specimen acquisition) for Gram stain and culture
   - MRSA colonization swabs
   - If immunocompromised and clinically indicated, ET aspirate, bronchoscopy (if required) or induced sputum for PJP
   - For remdesivir compassionate application: ALP, GGT, urea, INR/PTT

3. Monitoring considerations:
   - Remdesivir: daily monitoring of Cr, ALT, AST
   - Weekly COVID-19 nasopharyngeal swab PCR or COVID-19 Aptima swab
   - Repeat ECG for QTc monitoring if multiple QT prolonging agents in addition to hydroxychloroquine
ANTIVIRAL THERAPEUTIC CONSIDERATIONS

These investigational treatments may be considered in laboratory-confirmed COVID-19 infection (or ‘highly suspected’ and expected delay of lab confirmation > 24 hours) requiring hospitalization due to severe illness (see criteria page 3). Clinical progression typically occurs between 5-7 days after symptom onset. Risk factors for disease progression include older age and presence of underlying medical conditions (e.g. hypertension, diabetes, chronic lung diseases, and immunocompromised state). However, younger, previously healthy individuals can develop severe illness.

COVID-19 Antiviral Therapy Options

To date, there is no proven therapy for COVID-19 infection; based on available information, the working group prioritizes the following options for clinicians’ consideration (see the following for detailed rationale on current prioritization).

Infectious Diseases (ID) in-person or phone consultation is required to access these therapies for COVID-19 patients.

In patients requiring hospitalization due to COVID-19 pneumonia, consider:

A. If critically ill and requiring mechanical ventilation consider:

Remdesivir*: 200 mg IV loading dose on day 1, followed by 100 mg IV daily for 9 days – Compassionate access program (https://rdvcu.gilead.com/)

- Treatment with an alternate agent should be considered while awaiting request approval (may take 2-7 days)
- Gilead Sciences approval is based on inclusion/exclusion criteria (see https://rdvcu.gilead.com/)
- Once initiated, consider discontinuing other antiviral agents to preserve supply or as directed by Gilead

*Please note that as of March 22, 2020, Gilead is transitioning from individual compassionate use requests for remdesivir to expanded access programs, details of which are forthcoming. In the interim, remdesivir compassionate use requests have been restricted to pregnant women and children under 18 years with confirmed COVID-19 and severe manifestations of disease

Hydroxychloroquine (Plaquenil): 400 mg PO bid on day 1 then 200 mg PO bid for 4 days (may be started concurrently with remdesivir process)

- Note the data are limited; reasonable tolerance and safety profile
- 5 day course results in prolonged effect (long half-life)
- Contraindications – retinopathy, QTc prolongation
- If patient develops rash, discontinue therapy

B. In hospitalized patients not requiring mechanical ventilation, and with < 12 days of symptomatic illness, consider:

- lopinavir/ritonavir (Kaletra): 400-100 mg PO bid for 10-14 days (due to limited supply, ID may consider a shorter course)

OR (unrestricted by duration of illness)

- Hydroxychloroquine (Plaquenil): 400 mg PO bid on day 1 then 200 mg PO bid for 4 days

Note: There are no current supportive data for combination therapy so not currently recommended by the Working Group.

Other investigational regimens reviewed (prioritization not feasible due to lack of information):

- High dose steroid therapy – discouraged (may cause harm – worse outcomes in SARS and influenza)
- IVIG - discouraged (will not have neutralizing antibody and may worsen ARDS)
- Ribavirin as an adjunct to lopinavir/ritonavir (high dose has toxicity concerns, must be used in combination) - not recommended at this time
- 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 or compassionate use.

Last updated: March 22, 2020
Empiric Antimicrobial Therapy of Pneumonia in Hospitalized Suspect COVID-19 ADULT Patients

For patients who are pending confirmation COVID-19 positive / bacterial culture negative
**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 IV daily x 3 days (may be preferred in patients also on hydroxychloroquine, note QT interaction) OR Doxycycline 200 mg PO then 100 mg PO BID x 3 days

*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

(Alternate 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 and bacterial respiratory cultures are negative for MRSA

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

Oseltamivir 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

*Note: per Zhou et al, bacterial superinfection, which occurred in 29% of the reported Wuhan cohort, was defined as clinical symptoms or signs of pneumonia or bacteremia and a positive culture of a new pathogen obtained from lower respiratory tract specimens and/or blood culture.*

Culture directed therapy is preferred; Empiric therapy pending sputum/ET aspirate culture results:

**REASSESS at 48-72 hours WITH VIRAL AND 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.
Additional Care

1. **Avoid** nebulized medications and do not do bronchoscopy for obtaining specimens alone (ET aspirate preferred) to reduce aerosolization risk.


3. **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) pending further information it may be reasonable to prefer acetaminophen to NSAIDS for COVID-19 symptoms, but patients with inflammatory conditions on stable doses of NSAIDS could remain on them unless evidence changes.

4. If oxygen demand is increasing, **consider early referral for mechanical ventilation** as patient outcomes may be superior and planned intubations are at a lower risk for infection transmission than emergent ones.

5. **Other immune modulating therapies:**

There are many therapies that are being used or considered in trials or individual cases for which there remains limited or conflicting evidence (e.g., statins, Interferon β, tocilizumab, ribavirin, anakinra) and some with likely harm (e.g., high-dose methylprednisolone). The working group recommends that these therapies not be considered for routine use at this time outside possible clinical trials or compassionate use, until further evidence is available. The working group will continue to review the evidence and potential role of these therapies, and assessment of immunologic risk.

**Note:** steroids or IVIG (which would not have neutralizing antibody to SARS-CoV2) are NOT recommended. Steroids may blunt virus active cell mediated immunity, and IVIG could worsen ARDS and cytokine storm manifestations, and thus there is both a potential for harm and non-supportive observational clinical data.
Appendix 1: Rationale for Proposed Investigational Therapies

There is as of March 20, 2020 very little in vitro and even less in vivo evidence for treating COVID-19 infection directly. However, as SARS-CoV-2 has some genetic overlap with both MERS and SARS–CoV-1, several drugs with some putative activity against these other two coronaviruses were discussed. Agents that are no longer being manufactured (e.g. disulfiram) or on many months of back order (e.g. chloroquine) were not discussed in detail. Lopinavir/ritonavir (Kaletra), hydroxychloroquine (Plaquenil) are repurposed drugs discussed below, and remdesivir is an investigational agent of uncertain availability. All re-purposed drug options are considered weak antivirals against SARS-CoV-2, and as such, may be less likely to benefit critically ill individuals, but might be of more value early in disease or for those deemed at high risk for progression. Consult Infectious Diseases in person or by phone for consideration of any directed COVID-19 therapy.

When prescribing any therapy, it is recommended that drug Interactions are reviewed. Please consult your pharmacist, and/or see http://covid19-druginteractions.org/

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<thead>
<tr>
<th>Drug &amp; Dosage forms</th>
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<th>Monitoring</th>
<th>Comments</th>
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<td>400-100 mg PO bid for 10-14 days (due to limited supply, ID may consider a shorter course)</td>
<td>Major – QT prolongation and torsade de pointes (rare, high consequence)</td>
<td>Liver enzymes and lipase at baseline</td>
<td>Limited supply of tablets and oral solution available Administration: Tablets cannot be crushed. Oral solution should be given with food. Oral solution contains ethanol and propylene glycol and is incompatible with polyurethane feeding tubes but can be safely used with polyvinyl or silicone feeding tubes.</td>
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<td>200 mg - 50 mg tablet</td>
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<td>Dermatologic: common (low consequence)</td>
<td></td>
<td></td>
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<tr>
<td>80 mg/mL - 20 mg/mL oral solution</td>
<td></td>
<td>GI: diarrhea, vomiting &amp; abdominal pain (common, low consequence), pancreatitis (uncommon, high consequence)</td>
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<tr>
<td>Hydroxychloroquine (Plaquinil) (prodrug of chloroquine; chloroquine is not currently available in Canada) 200 mg tablet</td>
<td>400 mg PO bid x 1 day, then 200 mg PO bid for 4 days</td>
<td>Dizziness, headache, anorexia, nausea, vomiting, bloating, glucose abnormalities Most serious toxicities associated with long term use Serious: Retinopathy, LFT abnormalities, QT prolongation, hemolysis in G6PD deficient patients</td>
<td>Not required for short course</td>
<td>Limited supply of tablets available Potent inhibitor of SARS-CoV-2 in vitro. 5-day therapy results in sustained levels in lung tissue. There is a theoretic rationale to use hydroxychloroquine to prevent “cytokine storm”, however its role in therapy is not established. There may therefore be more of a role in earlier infection.</td>
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<tr>
<td>Remdesivir 100 mg vial</td>
<td>200 mg IV loading dose on day 1, followed by 100 mg IV once daily for 9 days See Gilead portal (<a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a>) for inclusion/exclusion criteria as these change frequently.</td>
<td>Elevated LFTs, hypotension during infusion Contraindicated in pregnancy and breastfeeding</td>
<td>Cr, ALT, AST daily</td>
<td>In addition to Gilead Sciences approval for compassionate access (<a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a>), Health Canada Special Access Program (SAP) patient-specific application is also required: <a href="https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs/remdesivir.html">https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs/remdesivir.html</a>) *Please note that as of March 22, 2020, Gilead is transitioning from individual compassionate use requests for remdesivir to expanded access programs, details of which are forthcoming. In the interim, remdesivir compassionate use requests have been restricted to pregnant women and children under 18 years with confirmed COVID-19 and severe manifestations of disease</td>
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Statement on Combination therapies:
The effect of combination antiviral therapy in COVID-19 patients is unknown. The working group, therefore, does not recommend combination therapy at this time due to lack of demonstrated advantage and potential excess consumption of limited drug supply. The use of combinations of lopinavir/ritonavir plus hydroxychloroquine OR remdesivir plus hydroxychloroquine have been reported in Italy, but there are no associated outcome data or anecdotal success. Combinations may have less evidence of benefit and may result in harm. Furthermore, if an adverse event occurs, identifying the offending agent is much more difficult.
## Appendix 2 Reference Table: Potential treatments* that have been studied for coronavirus infection and current recommendation (as of Mar 22, 2020)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Summary of available evidence</th>
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<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>SARS: 1 non-randomized study reported add-on lopinavir/ritonavir (n=41) was associated with lower rates of death and ARDS (2.4% vs 28.8%) compared with corticosteroid-ribavirin alone. Follow-up analysis (n=75) reported benefit limited to early initiation (median 5.5 days from onset). Reduced HCW infection in MERS prophylaxis. COVID-19 RCT: insignificant trends on illness duration (-1 day), and mortality (16.7% vs 25.0%) reduction vs SOC; late initiation (median 13 days).</td>
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<tr>
<td>Remdesivir</td>
<td>Limited efficacy/safety data in Ebola disease; reduces viral load and lung damage in MERS-CoV mice models if given early, superior to lopinavir/ritonavir/IFN; case reports/series on COVID-19, no efficacy data.</td>
</tr>
<tr>
<td>Chloroquine / Hydroxychloroquine</td>
<td>In vitro data show antiviral activity; influenza prevention trial show negative result. Potential toxicity and immunomodulation. Unpublished clinical data on hydroxychloroquine (+ macrolide) showed viral suppression.</td>
</tr>
<tr>
<td>Interferons</td>
<td>SARS: 1 non-randomized study reported add-on interferon (n=9, given at a median of 8 days from onset) was associated with faster resolution of pneumonia and improvement in oxygenation, compared with corticosteroid-ribavirin alone. MERS: 1 non-randomized study (n=144) reported no clinical benefit with interferon-ribavirin.</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>SARS: systematic review of 30 clinical studies reported inconclusive benefit and possible harm (e.g. hemolytic anaemia). In vitro synergism with lopinavir/ritonavir.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>SARS: systematic review of 29 clinical studies reported inconclusive benefit and possible harm (e.g. secondary infections); one randomized-controlled trial reported slower viral clearance. MERS: 1 non-randomized study (n=151) reported no clinical benefit, and slower viral clearance.</td>
</tr>
<tr>
<td>Combination of agents</td>
<td>Insufficient data for review.</td>
</tr>
</tbody>
</table>

*(only those agents with human data available are included; in vitro inhibition have been shown for ribavirin, lopinavir/ritonavir, interferons α/β and remdesivir). SOC = Standard of Care


Additional resource: bibliography and review found at [https://pubs.acs.org/doi/10.1021/acscentsci.0c00272](https://pubs.acs.org/doi/10.1021/acscentsci.0c00272)

Submitted by Dr. Lynora Saxinger, Dr. Nelson Lee, Dr. John Conly, Dr. John Gill on behalf of the COVID-19 Antimicrobial Management Working Group and reviewers (Critical Care, Infectious Diseases, Pharmacy, Emergency Medicine, Immunology).

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