Unproven Therapies for COVID-19

March 24, 2020

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Situation

SARS-CoV-2 (aka 2019-nCoV), the virus that causes the clinical illness COVID-19, is a novel RNA virus belonging to the coronavirus family. With hundreds of thousands of cases worldwide, various treatments are being used clinically or undergoing evaluation. In preparation for in-patient treatment of COVID-19 at BC’s health care facilities, the COVID Guidelines Committee has reviewed the evidence for these therapies and made recommendations concerning their use in consultation with various groups such as Infectious Diseases, Medical Microbiology, Intensive Care, Internal Medicine, Emergency Medicine, Hospitalists, LTC and Pharmacy. The Guidelines Committee has also provided general treatment guidelines for anti-infective use in the setting of viral pneumonia in in-patients. As this is an evolving situation, as emerging information becomes available we will make the necessary amendments to this SBAR along with up-to-date recommendations weekly, and as needed.

Background

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV-1). SARS-CoV-2, the virus responsible for the COVID-19 pandemic is a non-segmented, positive sense RNA virus most closely related to SARS-CoV-1, with 82% nucleotide identity. There are currently no approved therapies for COVID-19, and no therapies have been robustly evaluated. The majority of published evidence that suggests treatments for COVID-19 is extrapolated from experience with SARS, MERS or limited to case-series. Randomized-controlled trials are ongoing, most notably with two agents, an antiretroviral lopinavir/ritonavir (Kaletra®) used for treatment of HIV, and a novel investigational antiviral remdesivir. Non-randomized smaller studies, mainly from China, have included a variety of drugs, with Chinese Medicine research comprising over half of the studies. In vitro data and animal studies of various agents, mainly for the treatment of SARS, have also been published. A large proportion of the discussion regarding potential treatment for COVID-19 within the medical community has been occurring through non-academic channels such as social media, blogs or the news.
A scientific literature search of potential non-vaccine therapies for COVID-19 and other coronaviruses (search strategy below) resulted in over 200 publications citing the following potential pharmaceutical agents in order of frequency of appearance:

- lopinavir/ritonavir (Kaletra®)
- remdesivir
- chloroquine/hydroxychloroquine
- oseltamivir
- ribavirin and interferon
- tocilizumab
- corticosteroids
- antibiotic therapy
- NSAIDs/Ibuprofen
- ACE inhibitors and ARBs
- VTE prophylaxis

Non-medical sources have also listed a dozen of other agents, including ASC09, anakinra, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab and thymosin, among others. These agents were not found using a search of PubMed, Medline or Embase for the treatment of coronaviruses, but limited information was available online through, for example, study protocols.

Articles commenting on safety of other agents, for example ACE-inhibitors and NSAIDs in the context of COVID-19 have also been published.

Expert bodies such as the World Health Organization (WHO), the Society of Critical Care Medicine’s (SCCM) Surviving Sepsis Campaign, The Australian and New Zealand Intensive Care Society (ANZICS), and the Centers for Disease Control (CDC) have made recommendations for treatment of COVID-19 but they are limited to supportive care. Both support the enrollment of patients in clinical trials for currently unproven therapies. The WHO updated their guideline document regarding clinical management of severe COVID-19 on March 13, 2020, with a main recommendation of “Investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials.”

Locally, in British Columbia, while there is no formal consensus between clinician groups regarding treatment of COVID-19 with unapproved therapies, an informal agreement has been made between the clinicians at Vancouver Coastal and Providence Health that no treatment will be employed unless part of a randomized controlled trial. All proposed treatment approaches across the province have been obtained through personal communication. Many Health Authorities have committed to enrolling in an RCT of lopinavir/ritonavir (Kaletra®) called CATCO - A Multi-centre, Adaptive, Randomized, Open-label, Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. This RCT, led by Srinivas Murthy from BC Children’s Hospital and funded through the Canadian Institutes of Health Research, is currently undergoing Operational Approval after Harmonized Ethics Approval in the province was granted. Currently, Abbvie, the manufacturer of Kaletra®, will supply the study medication. Vancouver Coastal and Providence have informally stated that no treatment would be employed for inpatients with COVID-19 outside of this trial.
Assessment

Lopinavir/Ritonavir (Kaletra®)

Recommendation: Recommend against the routine use of lopinavir/ritonavir outside a randomized-controlled trial.

Lopinavir/ritonavir is a combination of antiviral agents used in treatment of HIV. Lopinavir is the effective agent that inhibits the protease activity of coronavirus; ritonavir increases the half-life of lopinavir. Lopinavir/ritonavir has the advantage that it is available in Canada, and has an established toxicity profile. In BC, the agent is non-formulary and mostly obtained through the Centre for Excellence for the treatment of HIV. At this time, it is listed as a “No Stock Available” item from wholesale due to countrywide allocation, but it could potentially be obtained through other channels. Ribavirin may be synergistic when added to lopinavir/ritonavir, especially in other coronaviruses. However, most clinical data for COVID-19 does not support the routine addition of ribavirin. Oral ribavirin is available in Canada, and is currently non-formulary. Inhaled ribavirin is restricted to the treatment of RSV, but has not been evaluated for the treatment of coronaviruses.

Human Data

Cao 2020: Randomized Controlled Trial of 199 patients with COVID-19 treated in Wubei, China at the peak of the outbreak
- 100 patients were randomized to receive lopinavir/ritonavir for 14 days and 99 to receive standard of care
- Patients included were those who had difficulty maintaining O2 saturations of >94% on room air; many patients were severely ill and received treatment late as evidenced by the nearly 25% mortality.
- The primary outcome was clinical improvement by 2 points measured by a 7-point ordinal scale, or discharge from hospital, whichever came first.
- The trial did not find a difference between the two groups in the primary outcome. Viral shedding was no different between groups. Mortality was lower in the treatment arm but was not statistically significant.
- 13.8% of patients in the treatment arm had to stop the drug because of adverse-effects such as gastrointestinal intolerance and laboratory abnormalities; but serious adverse events were more common in the control arm.

Young 2020 Cohort study describing 16 COVID-19 patients in Singapore.
- Among 6 patients with hypoxemia, five were treated with lopinavir/ritonavir (200 mg/100 mg BID, which is half of the usual dose of lopinavir).
- Among the 5 patients, 2 patients deteriorated and had persistent nasopharyngeal virus carriage.
- The authors of the study suggested that perhaps ribavirin should have been used in addition

Kim 2020 & Lim 2020: Lopinavir/ritonavir has been used to treat two individual case report patients with COVID-19 in South Korea

Park 2019: Retrospective cohort study on post-exposure prophylaxis against MERS
- This is a retrospective cohort study involving 22 patients with high-risk exposure to a single MERS patient). As a control group, four hospitals with outbreaks of MERS were selected. Post-exposure prophylaxis consisted of a combination of lopinavir/ritonavir (400 mg / 100 mg BID for
11-13 days) plus ribavirin (2000 mg loading dose, then 1200 mg q8hr for four days, then 600 mg q8hr for 6-8 days).
- MERS infections did not occur in anyone treated with post-exposure prophylaxis. However, the manner in which the control group was selected likely biased the study in favor of showing a benefit of post-exposure prophylaxis.
- Post-exposure therapy was generally well tolerated, although most patients reported some side effects (most commonly nausea, diarrhea, stomatitis, or fever). Laboratory evaluation shows frequent occurrence of anemia (45%), leukopenia (40%), and hyperbilirubinemia (100%).

Chu 2004: Open-label before/after study on SARS
- 41 patients treated with lopinavir/ritonavir plus ribavirin were compared to 111 historical control patients treated with ribavirin alone. Poor clinical outcomes (ARDS or death) were lower in the treatment group (2.4% vs. 29%). These differences persisted in multivariable models, which attempted to correct for baseline imbalances between the groups.
- Use of lopinavir/ritonavir use correlated with a dramatic reduction in viral load.
- All patients received concomitant ribavirin.
- One patient discontinued the medications due to doubling of liver enzymes

Chan 2003: Retrospective matched multicenter cohort study on SARS
- 75 patients treated with lopinavir/ritonavir were compared with matched controls.
- Up-front treatment with lopinavir/ritonavir combined with ribavirin correlated with reduced mortality (2.3% versus 16%). However, rescue therapy with lopinavir/ritonavir (often without concomitant ribavirin) showed no effect.
- Study reported that the drug was “well tolerated” and side effects were minimal.

Animal Data
Chan 2015: Lopinavir/ritonavir was effective against MERS-CoV in a primate animal model

In-vitro Data
In-vitro activity against SARS
- Lopinavir showed in vitro antiviral activity against SARS at concentration of 4 ug/ml. However, when combined with ribavirin, lopinavir appears considerably more effective (with an inhibitory concentration of 1 ug/mL) (Chu 2004).
- For reference, the peak and trough serum concentrations of lopinavir are 10 and 5.5 ug/ml

There are no reported in vitro studies of COVID-19.

Drug interactions with protease-inhibitors are well known and limit their use. Patients receiving interacting therapies such as apixaban, rivaroxaban, dabigatran, cyclosporine, tacrolimus, methadone, and amiodarone may not be candidates for treatment with Kaletra.

Remdesivir
Recommendation: Recommend against the routine use of Remdesivir outside a randomized-controlled trial.

Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity. It was initially developed and evaluated for the treatment of Ebola. It inhibits RNA-dependent RNA polymerase, which
is 96% identical in sequence between MERS, SARS and COVID-19. Remdesivir has demonstrated in vitro and in vivo activity in animal models against the viral pathogens MERS and SARS (Sheahan 2020).

Unfortunately, remdesivir is not commercially available and not approved by the FDA yet. Remdesivir was used on the basis of Compassionate Use for one of the first patients with COVID-19 in the United States (Holshue 2020). The patient improved rapidly with 7 days of treatment and no adverse effects. Viral PCR was negative for the virus after one day of therapy.

Remdesivir is being used in several stage 3 trials in the United States being sponsored by NIAID. Enrollment in this trial seems like a desirable approach to antiviral therapy but is not feasible in Canada at this time. There are four other trials registered worldwide.

The process of obtaining remdesivir in Canada for Compassionate Use (CU) outside of the abovementioned RCT has been verified with the company (Gilead) and Health Canada. It consists of a multi-step process that includes an application on the Gilead website, as well as a Special Access Program (SAP) application to Health Canada. Our estimates are that obtaining the drug would take days and is not guaranteed. Personal communication confirmed that one group in Edmonton attempted to get remdesivir for compassionate use; it was never released from the company or received. The inclusion criteria for the use of remdesivir seem prohibitive; patients need to be diagnosed with severe, virologically confirmed disease failing supportive care, on ventilatory support but not receiving vasopressor support or experiencing organ failure. Application for SAP and CU may be considered if the eligibility criteria are met. Gilead states on their website that stock is limited and we were unable to verify if the drug would be provided free of charge. There are also changes coming to the Gilead program. The compassionate use program is transitioning to an expanded access program. It is unclear how this will affect access in Canada to remdesivir.

**Chloroquine/Hydroxychloroquine**

**Recommendation:** We recommend against the use of chloroquine and hydroxychloroquine for treatment or prophylaxis outside of a clinical trial.

Chloroquine and hydroxychloroquine are generally used for treatment of malaria, amebiasis and certain inflammatory conditions like rheumatoid arthritis. It has anti-viral activity in vitro, but no established clinical efficacy in treatment of viral disease. Chloroquine/hydroxychloroquine appear to work via multiple mechanisms including glycosylation of the ACE2 receptor thereby decreasing SARS-CoV-2’s ability to enter cells, impairment of acidification of endosomes which interferes with virus trafficking within cells, and immunomodulatory effects which may attenuate cytokine storm reactions in severe disease. However, it should be noted that immunosuppressive actions may be harmful in viral disease.

Chloroquine is currently unavailable for order in Canada. Hydroxychloroquine is currently available in Canada and is on the BC provincial formulary. However, due to strong global demand of hydroxychloroquine after President Trump’s press release on March 19, 2020 describing the drug as a “game changer”, supply chain issues of hydroxychloroquine should be regarded as unstable.

The safety of hydroxychloroquine has not been assessed in the treatment of coronavirus infections. However, in general hydroxychloroquine is well tolerated based on experience with its use in patients with malaria and rheumatoid arthritis. Common side effects include gastrointestinal intolerance. Less common side effects to monitor include hypoglycemia and skin reactions. Other reported toxicities that are rarely encountered clinically include QT prolongation, bone marrow suppression, and hepatotoxicity.
Retinal toxicities are a known adverse effect of hydroxychloroquine but typically described after years of prolonged use.

**Human Data**
In a small case series of 26 hospitalized patients in France (Gautret 2020) received hydroxychloroquine 200 mg three times per day for 10 days; 6 of these patients received azithromycin. The primary endpoint was virological clearance on day 6. The trial compared the primary outcome to 16 controls who refused to participate or were treated at another center. Some patients in both groups were asymptomatic. The study reported that COVID-19 PCR was negative on 100% of patients on day 6 who took both drugs, 57.1% in those who received hydroxychloroquine alone and 12.5% of those who did not receive treatment. However, 6 patients treated with hydroxychloroquine were excluded from the analysis as viral samples were unavailable due to transfer to ICU, discharge home, treatment cessation, or death. No clinical endpoints were reported and the endpoint for negativity was a CT value >35 which differs from typical virological studies. The main limitations of this study include its non-randomized nature and lack of blinding which introduces selection, performance and detection bias. In addition, loss to follow-up was significant. Due to these factors, any meaningful clinical conclusions from this study cannot be derived.

A Chinese report states that chloroquine use in 100 patients “is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course” but patient data was not reported (Gao 2020). No other publication providing patient data pertaining to this study has been found. The study’s author was emailed for detailed patient data and the group is awaiting response.

An expert consensus group in Guangdong China is recommending chloroquine phosphate 500 mg bid x 10 days for all patients with COVID-19 without contraindications to chloroquine (Jiang Shanping 2020). No clinical evidence was provided to support this recommendation. There are multiple trials listed on the Chinese Clinical Trial Registry regarding chloroquine and hydroxychloroquine; no data from these trials has been published in peer-reviewed journals. As of March 22, 2020, there are at least 5 clinical trials of hydroxychloroquine in various stages of development.

**Animal Data**
Chloroquine did not reduce viral replication in mice infected with SARS (Bernard 2006).

**In-vitro Data**
In-vitro data using Vero cells shows that chloroquine can inhibit COVID-19 with a 50% effective concentration (EC50) of 1 μM, implying that therapeutic levels could be achieved in humans with a 500 mg dose (Wang 2020). The EC50 of chloroquine for SARS is 4.4 to 8.8 μM (Colson 2020), suggesting that chloroquine could be more effective against COVID-19 than SARS.

Hydroxychloroquine might be more potent for COVID-19 than chloroquine. Hydroxychloroquine’s EC50 is 0.72 μM for COVID-19 (Yao 2020). Based on pharmacokinetic modelling, the study recommended a dose for hydroxychloroquine 400 mg twice daily x 1 day, then 200 mg twice daily x 4 days for treatment of COVID-19, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days (Yao 2020).

**Oseltamivir**
**Recommendation:** Recommend against use of oseltamivir unless suspected or confirmed influenza infection.

Neuraminidase inhibitors do not seem to have activity against COVID-19 (Tan 2004). Initial empiric therapy with neuraminidase inhibitors could be reasonable during influenza season in critically ill patients, if there is concern that the patient might have influenza pneumonia. Such patients can have confirmatory nasopharyngeal swabs for influenza. Currently, in many locations, patients presenting with viral pneumonia are much more likely to have influenza than COVID-19. Otherwise, the role for oseltamivir specifically for COVID-19 is limited.

**Ribavirin and interferon**

**Recommendation:** Strongly recommend against use of ribavirin and/or interferon for risk of harm.

**Human Data**

There are no known clinical trials evaluating the efficacy and safety of ribavirin and/or interferon in COVID-19.

A multicenter observational study in 349 critically ill patients with MERS compared ribavirin and interferon to controls who did not receive either therapy (Arabi 2019). Unadjusted 90-day mortality rates were higher in the treatment group (73.6%) versus controls (61.5%) p = 0.02. The adjusted analysis showed no difference between the two groups. Additionally, ribavirin and interferon treatment was not associated with more rapid viral clearance.

From experience in treatment of hepatitis C, ribavirin is well known to be a poorly tolerated drug. Flu-like symptoms and nausea develop in nearly 50% of patients and lead to premature discontinuation of hepatitis C treatment. Hemolytic anemia is a black box warning for ribavirin. Regular monitoring of CBC for anemia, leukopenia is required as ribavirin causes bone marrow suppression in a significant proportion of patients within 1 to 2 weeks of treatment. Ribavirin may also cause liver toxicity and dermatologic reactions.

**Tocilizumab**

**Recommendation:** Recommend against the routine use of Tocilizumab outside a randomized-controlled trial.

Tocilizumab is an anti-interleukin 6 monoclonal antibody used as immunotherapy for treatment of rheumatoid arthritis. While the maker of the drug, Sanofi is currently in discussion with the FDA to initiate trials for treatment of COVID-19, evidence for the use of this medication is limited to unpublished case-reports. For example, according to a blog post on the IDSA website, there is anecdotal evidence that the drug has been used in cases in China. Through google-translation, the blog stated that tocilizimab was used in cases of severe inflammatory response to COVID-19 with laboratory-proven high levels of IL6 (test only available via the Mayo Clinic at present). The Chinese medical community appears to support the drug to “control the cytokine storm” and “purify the blood” according to the IDSA blog. No medical journal has published a case or case series as of March 22, 2020. The theory behind this therapy is that this may treat a small select group of severe COVID-19 patients who develop features of hyperinflammation such as cytokine release syndrome (Mehta 2020). Additionally, a group retrospectively explored T-Cell levels in 522 COVID-19 patients. Given T-Cells are important for fighting viral infections, and the correlation between increasing levels of IL-6 and lower T-Cell counts, this group suggests exploring this pathway blockade in hopes of preventing further patient deterioration (Diao...
There exists early reports of its use in Italy as well. Several clinical trials are underway (NCT04317092, NCT04306705, NCT04310228). One is an RCT but the other are single arm intervention or parallel assignment without a placebo comparator. Other IL-6 antibody therapies are also being considered for clinical study (e.g. sarilumab; NCT04315298).

**Steroids**

**Recommendation:** Recommend against the use of steroids. However, steroids may be used if another compelling indication is present (e.g. asthma exacerbation, refractory septic shock).

There are no controlled clinical trials on the use of corticosteroids in COVID-19 patients or other coronaviruses (Alhazzani 2020). Surviving Sepsis Campaign Guidelines on the Management of Critically Ill Adults with COVID19 did an excellent review.

“A published, but not peer-reviewed, report of 26 patients with severe COVID-19 reports that the use of methylprednisolone at 1-2mg/kg/day for 5 to 7 days was associated with shorter duration of supplemental oxygen use (8.2 days vs. 13.5 days; P<0.001) and improved radiographic findings (Wang 2020). Although interesting, we judged these preliminary reports to be an insufficient basis for formulating recommendations, due to the risk of confounding. Therefore, we used indirect evidence from community acquired pneumonia, ARDS, and other viral infections to inform our recommendation.

There are several RCTs on the use of systemic corticosteroids in hospitalized patients with community acquired pneumonia, mostly non-ICU patients, some with sepsis or septic shock. A systematic review and meta-analysis of RCTs showed that using corticosteroids may reduce the need for mechanical ventilation (5 RCTs; 1060 patients; RR 0.45, 95% CI 0.26 to 0.79), ARDS (4 RCTs; 945 patients; RR 0.24, 95% CI 0.10 to 0.56) and the duration of hospitalization (6 RCTs; 1499 patients; MD -1.00 day, 95% CI, -1.79 to -0.21), but increase the risk of hyperglycemia requiring treatment (Lamontagne 2015). However, these trials included different populations, the effect on mortality outcome was unclear, and they used different drugs and dosing regimens. In addition, there are some concerns about corticosteroid use in viral pneumonias. Therefore, the results may not be generalizable to the COVID-19 population.

There are many published observational studies on the use of steroids in viral pneumonias (i.e. influenza virus, coronaviruses, and others), but they are prone to confounding, as sicker patients usually receive corticosteroids. We updated a recent Cochrane review on the use of corticosteroids in influenza (Lansbury 2015) and searched for studies on other coronaviruses. We included a total of 15 cohort studies on influenza and 10 on coronaviruses. Our meta-analysis of adjusted ORs showed an association between corticosteroid use and increased mortality (OR 2.76, 95% CI 2.06 to 3.69), but the effect in the patients with other coronaviruses was unclear (OR 0.83, 95% CI 0.32 to 2.17). Also, these studies are limited by significant heterogeneity. We found significant homogeneity between observational studies on the use of corticosteroids in ARDS caused by coronaviruses and in general viral ARDS (I2=82% and 77% respectively). Furthermore, in both cases, the summary statistic tended toward harm with the use of steroids.

We updated a recent Cochrane review (Lewis 2019) and identified an additional RCT (Villar 2020) dealing with ARDS. Overall, we included 7 RCTs enrolling 851 patients with ARDS. The use of corticosteroids reduced mortality (RR 0.75, 95% CI 0.59 to 0.95) and duration of mechanical ventilation (MD -4.93 days, 95% CI -7.81 to -2.06). However, these trials were not focused on viral ARDS, which limits the generalizability of their results to COVID-19 patients. In addition, we reviewed observational studies on corticosteroid use in viral ARDS, and identified 4 cohort studies. Although the point estimate showed
increased mortality, the CI included substantial harm and benefit (OR 1.40, 95% CI 0.76 to 2.57). In a recent RCT (INTEREST trial), the use of recombinant interferon β1b (rIFN β1ba) did not reduce mortality in ARDS patients, but in the subgroup of patients receiving corticosteroids, rIFN β1ba use was associated with increased mortality (OR, 2.53, 95% CI 1.12 to 5.72) (Ranieri 2020). The only direct evidence comes from a retrospective cohort study of 201 patients with COVID-19 pneumonia. This study showed an association between corticosteroid use and lower mortality in patients with COVID-19 and ARDS (HR 0.38, 95%CI 0.20 to 0.72). However, the estimate was not adjusted for confounding factors (Wu 2020).

The effect of corticosteroids in COVID-19 patients with sepsis or septic shock may be different. Recent systematic reviews and meta-analyses of RCTs in sepsis showed small improvements in mortality and faster resolution of shock with corticosteroid use, compared with not using corticosteroids (Rygard 2018, Rochwerg 2018, Lian 2019).

It is widely recognized that corticosteroids have a range of adverse effects. In viral pneumonia in the ICU, several studies showed an increase in viral shedding with corticosteroid use (Arabi 2018, Hui 2018, Lee 2004), potentially indicating viral replication, but the clinical implication of increased viral shedding is uncertain.”

**Antibiotic Therapies**

**Recommendation:** If bacterial infection is suspected antibiotics should be initiated based on institutional antibiograms and sensitivities.

**Initial Therapy**

As with any viral pneumonia, COVID-19 itself is not an indication for antibiotics. However, patients who present with respiratory symptoms and pulmonary infiltrates on imaging may meet the diagnostic criteria for pneumonia. Co-infection with a bacteria pathogen can be possible, and as per standard CAP therapy, antibiotics are indicated. An example of standard therapy for in-patient treatment for community acquired pneumonia is ceftriaxone 1-2 g IV daily with a macrolide, usually azithromycin 500mg IV x 3 days or azithromycin 500mg PO x 1 day followed by 250mg PO x 4 days. While patients infected with COVID-19 may have travel history or have come in contact with travelers, extending the spectrum of antimicrobials is not warranted unless the patient has significant risk factors for drug-resistant organisms. This is generally limited to health-care exposure in an area with high rates of antibiotic resistance in the last 90 days. Such patients should obtain an Infectious Disease consult for tailored antibiotic therapy.

De-escalating antimicrobials is usually possible in confirmed COVID-19 infection. Procalcitonin is a useful marker and is usually negative. This can be combined with other clinical features like lymphopenia, normal neutrophil count and lack of positive bacterial cultures. Based on these tests, antibiotics might be discontinued in <48 hours.

**Delayed Bacterial Infection**

Hospital and ventilator-associated pneumonia can emerge during the hospital stay. Among patients who died from COVID-19, one series found that 11/68 (16%) had secondary infections (Ruan 2020). Hospital-acquired infection may be investigated and treated according to current VAP/HAP guidelines.

**NSAIDs**

**Recommendation:** Recommend acetaminophen use preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.
On March 17, the World Health Organization recommended NSAIDs should be avoided for treatment of COVID-19 symptoms, after French officials warned that anti-inflammatory drugs could worsen effects of the virus. The warning by French Health Minister Olivier Veran followed a recent study in The Lancet medical journal that hypothesised that an enzyme boosted by anti-inflammatory drugs such as ibuprofen could facilitate and worsen COVID-19 infections. After two days of contemplation, the WHO reissued a statement on Twitter stating that there is no specific reason to avoid NSAIDs based on this data.

**ACE inhibitors and ARBs**

**Recommendation:** Recommend that patients on ACE inhibitors and ARBs continue these agents as indicated and not cease therapy solely on the basis of COVID-19.

COVID-19 uses the ACE2 enzyme to gain entry into human cells, and some reports state that those taking ACE-inhibitors or ARBs may experience an up-regulation of these enzymes. Theoretically, patients taking these medications may have increased susceptibility to the virus; however this has not been shown clinically. Various expert groups such as the Canadian Cardiovascular Society and Hypertension Canada issued statements that uncontrolled hypertension or heart failure for which these medications are used would put patients at increased risk of poor outcomes due to COVID-19 and recommended that these agents not be discontinued.

**Venous Thromboembolism (VTE) prophylaxis**

**Recommendation:** Suggest enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in hospitalized patients with COVID-19. This dose was selected to reduce clinician suspicion of incident VTE and potentially save health care resources with patient transport and minimize risk of COVID-19 transmission to staff and others.

Rates of VTE in hospitalized patients with COVID-19 are expected to be similar patients with inflammatory disorders or sepsis. All hospitalized patients with COVID-19 should receive pharmacologic VTE prophylaxis, unless contraindicated. Based on observational data, thrombocytopenia and coagulopathy are not expected from COVID-19 while D-dimer levels are typically elevated in 50% of COVID-19 patients (Guan 2020).

Currently, the standard VTE prophylaxis regimen is enoxaparin 40 mg SC daily. In specific populations (e.g. orthopedic trauma and spinal cord injury patients), enoxaparin 30 mg SC twice daily is often used. The potential benefits with a higher daily dose of prophylactic anticoagulation include a reduced clinical suspicion for incident venous thromboembolism and, in turn, a lesser need for confirmatory radiologic procedures. This would result in reduced use of healthcare resources with patient transport and also lessen the risk of staff exposure and equipment contamination with COVID-19.

The half-life of enoxaparin based on anti-Xa activity is 4 to 6 hours so twice daily dosing aligns with the pharmacokinetics. From a logistics perspective, once daily dosing is more likely to be missed which would result in a patient unprotected for over 24 hours whereas twice daily administration ensures the evening dose is given even if the morning dose is held for procedures. Enoxaparin 30 mg bid dosing has shown to have similar bleeding risk as heparin 5000 units bid in orthopedic trauma patients and in spinal cord injury patients (Geerts 1996, SCI Investigators 2003).
Recommendations

1. Lopinavir / Ritonavir (Kaletra®)
   **Recommendation:** Recommend against the routine use of lopinavir/ritonavir outside a randomized-controlled trial (CATCO).

2. Remdesivir
   **Recommendation:** Due to limited efficacy data and restrictive access remdesivir is not recommended at this time.

3. Chloroquine and Hydroxychloroquine
   **Recommendation:** Recommend against the routine use of Chloroquine and Hydroxychloroquine outside a randomized-controlled trial.

4. Oseltamivir
   **Recommendation** Recommend against use of oseltamivir unless suspected or confirmed influenza infection.

5. Ribavirin and Interferon:
   **Recommendation:** Strongly recommend against use of ribavirin and/or interferon for risk of harm.

6. Tocilizumab
   **Recommendation:** Recommend against the routine use of tocilizumab at this time.

7. Steroids
   **Recommendation:** Recommend against the use of steroids. However, steroids may be used if another compelling indication is present (e.g. asthma exacerbation, refractory septic shock).

8. Antibiotic Therapies
   **Recommendation:** If bacterial infection is suspected antibiotics should be initiated based on institutional antibiograms and sensitivities.

9. NSAIDs/Ibuprofen
   **Recommendation:** Recommend acetaminophen use preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.

10. ACE inhibitors and ARBs
    **Recommendation:** Recommend that patients on ACE inhibitors and ARBs continue these agents as indicated and not cease therapy solely on the basis of COVID-19.

11. VTE prophylaxis
    **Recommendation:** Suggest enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in hospitalized patients with COVID-19. This dose was selected to reduce clinician suspicion of incident VTE and potentially save health care resources with patient transport and minimize risk of COVID-19 transmission to staff and others.
12. Other investigational therapies

**Recommendation:** Recommend against any other investigational agent, including ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab, thymosin, natural health products, and traditional Chinese medicines due to lack of data, lack of availability, or both.

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<tr>
<td>Dr Andrew Guy</td>
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SEARCH STRATEGY:


Search Databases: PubMed, Medline, Ovid

Search Date: March 19, 2020

REFERENCES:


