SUMMARY

This summary highlights the recommendations made by the Infection Management Advisory Committe on the antiviral treatment of COVID-19. These recommendations are based on an extensive literature review and collaboration with various experts and clinicians. The full document follows this page.

IMAC will be monitoring new evidence as it emerges and updating the recommendations as needed.

The full document also provides recommendations on management of bacterial infections and addresses recent controversies related to the use of steroids, NSAIDs and ACE Inhibitors in the context of COVID-19.

1. Lopinavir/ritonavir: We recommend against the routine use of lopinavir/ritonavir outside a randomized-controlled trial (e.g. CATCO).
2. Ribavirin and interferon: In light of insufficient evidence and potential adverse-effects, we advise against the use of ribavirin and interferon.
3. Remdesivir: While treatment with remdesivir remains promising, obtaining the drug for compassionate is not feasibile. We recommend against further attempts to obtain remdesivir. We recommend enrollment in a randomized-controlled trial of remdesivir if it becomes an option (e.g. adaptive arm of CATCO).
4. Hydroxychloroquine/chloroquine: Based on the lack of clinically convincing outcomes, safety concerns and the fragility of the supply chain, we recommend against routine use of chloroquine or hydroxychloroquine outside of a controlled trial. IMAC is committed to evaluating this particular therapy very closely. IMAC members recommended a temporary restriction of the drug to ensure it is used for approved indications.
5. Toculizimab/sarilumab: We were unable to evaluate any convincing evidence published in English that supports the use of anti-IL-6 agents. Although limited Chinese literature uses promising language, we currently cannot recommend routine its administration for COVID-19. We support the participation in clinical trials; however at this time significant operational and resource barriers exist with current study protocols.
6. Convalescent Plasma: The use of convalescent plasma warrants further study. We support the initiatives of the Canadian Blood Services and the CONCUR clinical trial in evaluating and operationalizing convalescent plasma therapy. We will evaluate trial opportunity on a case-by-case basis based on feasibility at VIHA.

7. Intravenous Immunoglobulin G: There is no evidence to support the use of intravenous immune globulin (IVIG) for the treatment of COVID-19 infection and it should not be used for this indication. It is critical to prioritize the use of IVIG for patients with established clinical indications to preserve the adequacy of its supply.
8. Other agents: We recommend against treatment with any other investigational agent, including ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab and thymosin due to lack of data, lack of availability, or both.

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PREPARED FOR:	Emergency Operations Center (EOC)
TOPIC:	Therapies for COVID-19
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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 approximately two million cases worldwide, various treatments are being used clinically or undergoing evaluation. In preparation for in-patient treatment of COVID-19 at Island Health facilities, the Infection Management Advisory Committee (IMAC) has reviewed the evidence for these therapies and made recommendations concerning their use in consultation with various VIHA groups such as Intensive Care, Internal Medicine, Hospitalists and Pharmacy. IMAC has also provided general treatment guidelines for anti-infective use in the setting of viral pneumonia in in-patients. In this rapidly evolving situation, as emerging information becomes available, IMAC will make the necessary amendments to this SBAR along with up-to-date recommendations regularly. As this document has also become the reference for the BCCDC position statement on COVID-19 therapies, this SBAR will be updated each Wednesday, and updates will be sent and harmonized with the BCCDC.

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 have been over a million cases of COVID-19 to date, with a global case fatality rate of ranging between 2% to 10% depending on the country and criteria for testing.

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 three agents, an antiretroviral lopinavir/ritonavir (Kaletra) used for treatment of HIV, a novel investigational antiviral remdesivir and the monoclonal antibody tocilizumab used for rheumatoid arthritis. Hydroxycholoroquine has also been an agent of particular interest due to its in-vitro antiviral activity, especially for milder disease or prophylaxis. 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 hundreds of publications citing the following potential pharmaceutical agents in order of frequency of appearance:

- lopinavir/ritonavir
- chloroquine/hydroxychloroquine
- ribavirin
- remdesivir
- oseltamivir and other neuraminidase inhibitors
- tocilizumab/sarilumab
- convalescent plasma
- IVIG
- steroids
- antibiotic therapy

Non-medical sources have also listed a dozen of other agents, including ASC09, azvudine baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab, ivermectin, arbidol and thymosin, among others. Most of 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 Center 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, there is consensus between groups regarding treatment of COVID-19 with unapproved therapies through the BCCDC's Clinical Reference Group, Provincial Antimicrobial Committee of Experts (PACE) and the clinical community. The BCCDC statement and SBAR, updated weekly, is representative of the consensus in the province:

"There are no proven therapies for the prevention or treatment of COVID-19. All agents have the possibility of associated harm, and pharmaceutical supplies province-wide and nationally for many of the possible agents are severely limited. It is recognized that compassionate use of drugs will be pursued for ill patients with no known therapy. Ideally, use of these agents would be through a controlled clinical trial so as to better inform practice; in the absence of research studies, patients should be aware of the risks and benefits of novel therapies, and safety data collected to inform the larger community."

"Within British Columbia the use of specific antivirals outside of clinical trials is NOT recommended."

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 has now been adapted to include two additional study arms to simultaneously evaluate remdesivir and hydroxychloroquine. This RCT, led by Shrin Murthy from BC Women's and Children's and funded through

the Canadian Institutes of Health Research, is currently undergoing Operational Approval after Harmonized Ethics Approval in the province was granted. The manufacturers of the respective drugs would be supplying the study medications. At VIHA, Dr. Daniel Ovakim (Intensivist; VIHA PI), Dr. Gordon Wood (Intensivist, co-investigator) and Dr. Eric Partlow, (Infectious Disease Physician; co-investigator) have volunteered to be the local investigators for CATCO. The clinical trials support team from Intensive Care has been engaged and is awaiting operational approval after obtaining a harmonized ethics approval of the protocol. Enrolling patients at other sites across the Island is being explored and is largely based on operational ability (e.g. having enough clinicians with necessary training to give consent).

Several other trials are in the process of recruiting sites across Canada and are in various stages of ethics and operational approval. These studies include evaluation of sarilumab and toculizumab in treating cytokine storm, hydroxychloroquine prophylaxis in healthcare workers and contacts, use of convalescent plasma, and the use of colchicine in infected outpatients. Island Health is reviewing the local feasibility of these clinical studies on a daily basis.

Assessment

Lopinavir/Ritonavir (Kaletra) with/without Ribavirin

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 Clinical Data

Cao at al. 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 slightly lower in the treatment arm but was not clinically or 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.

Young et al. 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

Lopinavir/ritonavir has been used to successfully treat one patient with COVID-19 (Kim 2020).

Small Case-series for COVID-19 (Wang 2020)

- Four patients with COVID-19 were given antiviral treatment including lopinavir/ritonavir.
- After treatment, three patients showed significant improvement in pneumonia-associated symptoms, two of whom were confirmed to be COVID-19 negative and discharged, and one of whom was negative for the virus at the first test.

Larger Retrospective Study for COVID-19 (Chen 2020)

- A retrospective study enrolled 134 patients revealed that there is no significant difference between LPV/r-treated group (n=52), Abidol-treated group (n=34), and control group (n=48) in improving symptom or in reducing viral loads.
- The negative rate of COVID-19 nucleic acid on the 7 day was 71.8%, 82.6%, and 77.1%, respectively (P=.79).

Chu et al. 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 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 et al. 2003: Retrospective matched multi-center 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.

Park et al. 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%).

Nine randomized controlled trials of lopinovir/ritonavir in patients with COVID-19 have been registered in China up to February 22, 2020, and two trials in North America, including the Canadian CATCO trial in which VIHA is participating. Currently, the combination of lopinavir/ritonavir is a recommended antiviral regimen in the latest version of the Diagnosis and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China.

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 et al. 2004).
- For reference, the peak and trough serum concentrations of lopinavir are 10 and 5.5 ug/ml
- An analysis of molecular dynamics simulations showed that the SARS-CoV 3CLpro enzyme could be inhibited by the combination of lopinavir and ritonavir. (Nukoolkarn 2008).
- A binding analysis of the main coronavirus proteinase with lopinovir showed that half of lopinavir is left outside the catalytic site, and the efficacy of lopinavir may be poor (Zhang 2004).
- Another study showed that neither lopinavir nor ritonavir has an effect on the replication of SARS-CoV (Yamamoto 2004).

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

Animal Data

Lopinavir/ritonavir was effective against MERS-CoV in a primate animal model (Chan 2015).

Safety

Diarrhea, nausea, and asthenia are the most frequently reported reactions in patients receiving lopinavir therapy for treatment of coronaviruses (Hurst 2000). Elevated total bilirubin, triglyceride, and hepatic enzyme levels have also been reported. A retrospective study of MERS showed that the most common symptoms and laboratory tests of lopinavir/ritonavir were diarrhea (40.9%), nausea (40.9%), stomatitis (18.2%), fever (13.6%), anemia (45.0%), leukopenia (40.0%), and hyperbilirubinemia (100%) (Park 2019). However, the symptoms and laboratory tests returned to normal after lopinavir therapy ceased. In the 2020 RCT by Cao et al. 13.8% of patients needed to stop lopinavir/ritonavir due to adverse effects, but no ADR was considered serious. Drug interactions with protease-inhibitors are well known and limit their use. Patients receiving interacting therapies such as amiodarone, certain statins and benzodiazepines, rifampin, among others are generally not candidates for treatment with lopinavir/ritonavir.

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. Regular monitoring of CBC for hemolytic anemia, leukopenia and dose adjustment may be required for toxicity as ribavirin causes bone marrow suppression in many after 2-4 weeks of treatment. Ribavirin may also cause liver toxicity and transaminitis.

Remdesivir

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 and others).

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. Since then, a case series of patients receiving remdesivir as part of the compassionate use program has also been published in the NEJM.

Grein J. et al. 2020: Analysis of 53 patients who received remdesivir as part of Gilead's compassionate access program in the US, Europe or Japan.

- Patients were eligible to receive a 7-ady course of remdesivir if they had oxygen saturation of 94% or less while on room air or who were receiving oxygen support. 64% of patients were on invasive mechanical ventilation at drug initiation. The approval process and selection of patients for the compassionate use program was not described.
- Patients received remdesivir, on average, 12 days after illness onset.
- At a median follow-up of 18 days, 68% of patients were reported to have improvement in their oxygen support needs; 57% of ventilated patients were extubated.
- Mortality at time of publication was 13% and authors suggest that this is less than what has been reported in other cohorts of hospitalized patients.
- Due to potential bias in patient selection, lack of control group, absence of pre-specified outcomes, and authorship attributed to the drug's manufacturer, this analysis, along with the publishing journal (NEJM) has received numerous criticisms within the medical community.

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

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. At VIHA, an application was filed for CU for the first patient admitted to the RJH ICU on March 20, 2020. While approval was granted the same day by Gilead and Health Canada, the drug never arrived. Personal communication confirmed that one group in Edmonton attempted to get remdesivir for compassionate use four times with the same result. The inclusion criteria

for the use of remdesivir seem prohibitive; patients need to be diagnosed with severe, virologically confirmed disease failing supportive case, on ventilator support but not receiving vasopressor support or experiencing organ failure. Gilead states on their website that stock is limited and we were unable to verify if the drug would be provided free of charge. At this time, further applications for CU and SAP are unlikely to produce the drug in a timely manner and should not be attempted.

Chloroquine/Hydroxychloroquine

Chloroquine/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 interference with cellular receptor ACE2 (potentially making it particularly effective against SARS and COVID-19) and impairment of acidification of endosomes, which interferes with virus trafficking within cells. It also has 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. Various professional groups including the FDA, Ontario Medical Association and Ontario Pharmacists Association have released statements discouraging the off-label use of hydroxychloroquine and imploring the medical community to reserve the supply for those who take it for evidence-based indications.

Disconcerting safety reports have emerged since Trump's press release. A couple from Arizona have ingested an aquarium-cleaning agent containing chloroquine for prophylaxis leading to one death and one serious hospitalization. There have also been reports of severe overdoses leading to cardiac toxicity in Africa, where the agent is routinely used for malaria. The safety of hydroxychloroquine has not been

assessed in the treatment of coronavirus infections. In general, hydroxychloroquine that is prescribed and monitored by health care provider is well tolerated based on experience with its use in patients with lupus 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

Tang et al 2020: randomized, open-label multi-center study at 16 hospital sites with 150 patients in China (non-peer reviewed publication but registered trial ChiCTR2000029868)

- Compared hydroxychloroquine 400 mg three times daily x 3 days, then 400 mg twice daily to complete 2 weeks (n=75) vs usual care (n=75)
- Trial originally planned to enrol 360 patients but the study was terminated early due to an interim analysis at 150 patients where the investigators found "promising results into clinical benefits that could save lives". This statement was based off a very small post-hoc subgroup analysis in patients who did not receive "antivirals" where hydroxychloroquine subgroup showed better symptom alleviation than control group: 8/14 vs 1/14; they also noted CRP was reduced more in the overall hydroxychloroquine group but the baseline CRP was higher in the hydroxychloroquine group and the actual differences in change from baseline were of questionable statistical and clinical significance: 6.99 vs 2.72 mg/L, p=0.045 (not adjusted for multiple comparisons)
- When looking at the entire study sample, there were no differences in its primary outcome of negative viral studies at any time point; there were also no differences in clinical symptoms at any time point
- More adverse effects were noted in the hydroxychloroquine group 30% vs 8.8%, p=0.001 and 2 patients in the hydroxychloroquine group developed serious adverse events
- Limitations of this study are numerous; the main limitations are its open-label nature (performance and detection bias) and the study's premature termination based on questionable interpretation of a small post-hoc subgroup analysis that showed weak and imprecise benefit for hydroxychloroquine; in addition, patients were enrolled into this study after a mean of 17 days

which leads us to question its generalizability; overall, this study does not offer credible evidence to support hydroxychloroquine use in treatment of hospitalized patients with COVID-19

Borba 2020: Preliminary safety results of a two centre RCT on chloroquine (CloroCOVID study), currently with 81 patients enrolled.

- The studies evaluated high dose chloroquine (600mg twice daily for 10 days or total dose 12g) compared to low dose chloroquine (450mg for 5 days, twice daily only on the first day, or total dose 2.7g)
- Patients also got ceftriaxone and azithromycin
- High dose chloroquine arm experienced more QTc>500ms (25%)
- Higher death trend was observed in high dose (17%) vs lower dosage.
- High dose arm no longer recruiting do to harm and no benefit

Mahevas et al. 2020: Analysis of data on outcomes of patients given hydrocychloroquine matched to retrospective controls.

- Non-peer reviewed, unpublished manuscript posted on the medRXiv website
- Reports data on 181 patients with COVID-19 treated in 4 French hospitals who required oxygen via nasal prongs at time of presentation
- 84 patients who received hydroxychloroquine within 48 hours of admission were selected for analysis and matched to 97 patients who did not, using 19 variables (e.g. demographics, co-morbidities and clinical criteria) that comprised a propensity score
- Groups were evenly matched for COVID-19 severity (96.1% match rate)
- Exclusion criteria were dialysis, treatment with lopinavir/ritonavir, remdesivir or IL-6 inhibitors
- No apparent difference between groups was observed:
    - Primary endpoint was ICU admission or death at day 7 from admission occurred in 20.2% of patients in the treatment group vs. 22.1% in comparator group
    - 3 vs. 4 patients died comparing treatment vs. non-treatment (NS)

  - ARDS rate at 7 days was 27.4% vs. 24.1% respectively
  - 9.5% of patients treated with hydroxychloroquine needed to stop treatment due to electrocardiogram changes
- Limitations include non-randomized nature, potentially missed variables during matching, variance in practice between hospitals and a small sample size
- The study, deemed as reasonably conducted, concluded that these results do not support the use of hydroxychloroquine in hospitalized patients with COVID-19.

Huang 2020: randomized, non-blinded, study of 22 hospitalized participants in Guangdong, China; published (uncorrected manuscript)

- Compared chloroquine 500 mg twice daily x 10 days (n=10) vs lopinavir/ritonavir 400/100 mg twice daily x 10 days (n=12)
- Did not report use of other agents like immunomodulators or steroids
- Outcomes were assessed at 14 days included viral clearance, lung clearance on CT scans, hospital discharge, and adverse events
- Study reported that 6 patients in the chloroquine group reached "lung clearance" on day 9 compared to 3 patients in the lopinavir/ritonavir group and that patients in the chloroquine group seem to "recover better"
- Limitations of this study include its non-blinded nature, seemingly sicker cohort of patients assigned to lopinavir/ritonavir (older, longer time from symptom onset to enrollment, higher SOFA scores, more patients with baseline CT findings of pneumonia), poor outcomes definitions, and non-inclusion of critically ill patients
- Due to small sample size and limitations mentioned above, no strong conclusions can be drawn from this study

Molina 2020: case series of 11 hospitalized patients in France

- All patients received hydroxychloroquine 600 mg daily for 10 days and azithromycin 500 mg on day 1, then 250 mg on days 2 to 5 (same dosing as original Gautret study listed below)
- 10/11 patients had fever and were on oxygen therapy

- 1 patient died, 2 transferred to ICU, 1 stopped therapy due to QTc prolongation by 65 ms
- 8/10 patients still tested positive in nasopharyngeal swabs at days 5 to 6 after treatment
- The study concluded that hydroxychloroquine made no impact on virological cure
- Limitations of this study include its very small sample size and its lack of control group

Chen 2020: randomized, non-blinded single-center clinical trial in Wuhan, China

- Non-peer reviewed but registered clinical trial (ChiCTR2000029559)
- Randomized 62 participants to hydroxychloroquine 200 mg twice daily for 5 days (n=31) or usual care (n=31); use of placebo was not reported in the manuscript. All patients received oxygen therapy, "antiviral agents", IVIG, with or without corticosteroids. Critically ill patients or those with severe end organ dysfunction were excluded.
- Time to defervescence was faster in the hydroxychloroquine group (2.2 vs 3.2 days); however, only 71% and 55% of the hydroxychloroquine group and control group had fever on day 0.
- 4 patients in the control group "progressed to severe illness"; this was not well defined
- This study also reported a higher proportion of patients in the hydroxychloroquine group achieved "more than 50% "pneumonia absorption" on CT scan compared to the control group (80.6% vs 54.8%).
- Limitations of this study include its overall small sample size, its non-blinded nature (performance and detection bias), major discrepancies between manuscript and registered trial protocol, use of IVIG and "anti-virals" in both groups, and its lack of generalizability to the North American population. In addition, the clinical endpoints in this study were of questionable relevance and the magnitude of benefit shown, if any, was not impressive.

Gautret 2020: case series of 80 hospitalized patients in a single-center in France

- Non-peer reviewed manuscript; no control group
- Recorded 80 cases of hospitalized patients with positive viral studies admitted to an infectious diseases ward where patients received hydroxychloroquine 200 mg three times per day for 10 days plus azithromycin for 5 days
- The average duration of symptoms prior to hospitalization was 5 days with a wide range (1 to 17 days) and 4/80 patients were asymptomatic (reasons for admitting these patients were not

reported). In general, patients were reasonably healthy with an NEWS score of 0 to 4 in 92% of cases. Only 15% of cases required oxygen therapy.

- This study reported 93% of participants had negative viral PCR at day 8. Viral cultures done in select patients were 97.5% negative by day 5.
- At the time of their writing, 1/80 patients died, 14/80 patients still hospitalized (3/80 patients admitted to ICU), and 65/80 patients discharged home.
- This study has numerous limitations including its lack of control group, its study population's overall lack of need for oxygen support which argues against need for hospitalization and antiviral treatment in the first place, and unclear clinical relevance of repeated viral PCR studies and cultures.

Chen 2020: randomized open-label single center pilot study (NCT 04261517); Shanghai China university journal; English abstract only; full article in Chinese

- Randomized 30 patients total (15 to each group) to hydroxychloroquine 400 mg daily x 5 days vs usual care. Both groups received conventional treatment of supportive care.
- All patients received nebulized interferon, over two-thirds received umifenovir (Arbidol), and a small proportion received Kaletra.
- Primary outcome was negative pharyngeal swab viral study on day 7 after randomization and no difference was observed between groups (hydroxychloroquine 13/15 (86.7%) vs usual care 14/15 (93%); NS)
- No difference was observed in secondary outcomes such as time to normothermia or radiographic progression on CT
- All patients showed improvement at follow-up exam
- Overall, this trial was a negative finding study with small numbers and with possible confounders due to co-treatments with interferon and umifenovir

Gautret 2020: Case-control series of 42 hospitalized patients in France with positive viral study

- 26 patients received hydroxychloroquine 200 mg three times per day for 10 days; 6 of these patients received azithromycin based on clinician preference.

- 16 patients who either refused to receive hydroxychloroquine or were treated at another center served as controls.
- The primary endpoint was virological clearance on day 6.
- 6 patients in the study were asymptomatic throughout the study.
- The study reported that COVID-19 PCR was negative in 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, its small sample size, its significant loss to follow-up (attrition bias), and lack of clinical outcomes. In addition, a significant proportion of patients were asymptomatic which argues against generalizability of study results.
- Due to limitations stated above, meaningful clinical conclusions from this study cannot be derived.

Chorin 2020: case series 84 hospitalized patients in New York taking hydroxychloroquine and azithromycin for COVID-19 to assess effects on QTc

- Average QTc prolonged from 435 (24) ms to 463 (32) ms at day 4, $p < 0.001$ measured on average 4 days after exposure
- 11% patients developed new QTc prolongation above 500 ms
- Renal failure was a major predictor of prolonged QTc; amiodarone was a weaker association
- No events of Torsades recorded including patients with QTc above 500
- This uncontrolled case series describes QTc prolongation occurring in hospitalized patients who take HCQ and azithromycin; 11% of patients experience QTc prolongation over 500 ms.

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 article is not available in English and this data could not be assessed. A news report stated that the study investigator cited that "120 patients treated with chloroquine phosphate developed critical illness, and 81 patients have been discharged so far." 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 for 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.

In-vitro Data

In vitro data using cell lines shows that chloroquine can inhibit COVID-19 with a 50% inhibitory concentration of 1 µM, implying that therapeutic levels could be achieved in humans (Wang 2020). The 50% inhibitory concentration of chloroquine for SARS is closer to 9 µM, suggesting that chloroquine could be more effective against COVID-19 than SARS (Al-Bari 2017).

A study published in Clinical Infectious Diseases suggested that hydroxychloroquine might be more potent for COVID-19 than chloroquine. The EC50=0.72 µM for hydroxychloroquine was found to be more potent than chloroquine (EC50=5.47 µM) in vitro. The study cited that "based on PK models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance" (Yao 2020).

Animal Data

Chloroquine failed to work in mice infected with SARS (Bernard 2006).

Convalescent Plasma

Convalescent plasma treatment refers to the process of drawing plasma, containing antibodies (mainly Ig-G) from patients who have recovered from a viral illness and administering that plasma to a patient infected with the illness. Also referred to as passive immunization, convalescent plasma has been used for over a century as attempted treatment for variety of infectious diseases including the Spanish Flu of 1918, Ebola and SARS.

Human Data

There is little evidence for the use of convalescent plasma in the treatment of COVID-19. Currently there are two case reports, a retrospective case series (n=5), and a prospective cohort study (n=20). Generally, authors report that patients treated with convalescent plasma appeared to experience improvement in clinical status and oxygen requirements, and successful weaning from mechanical ventilation. Due to the nature of the studies, there is high potential for selection bias and higher-quality data is needed.

Shen et al 2020: Case series of five critically ill patients in China requiring mechanical ventilation (one requiring ECMO).

- Patients received convalescent plasma from 5 recovered patients with Ig-G binding titers > 1:1000 on day 10 (N=1) or 20 (N=4) of their hospitalization
- All showed significant clinical improvements 2-4 weeks after receiving therapy in temperature, SOFA score, PaO2/FiO2, viral loads, neutralizing antibody titers and imaging findings
- ARDS resolved in 4/5 patients
- 3/5 patients weaned from mechanical ventilation within 2-weeks
- 1 patient on ECMO was weaned on day 5 post-transfusion
- As of Mar 25: 3/5 patients discharged; 2/5 patients in hospital in stable condition

Roback and Guarner followed the Shen et al. study by an editorial discussing the feasibility and limitations of using convalescent plasma. Some important limitations noted included the lack of a control group, use of multiple other therapies like steroids and antivirals and lack of clarity regarding optimal timing for plasma administration. The editorial also proposed several considerations that would need to be addressed to enable scaling convalescent plasma therapy to meet demand: These included strategies for donor recruitment, sample retrieval and storage, patient transfusion logistics and use of predictive modeling to manage donors and recipients. While useful, this editorial highlights the practical challenges of routine administration of convalescent plasma.

Duan et al 2020: Prospective feasibility pilot of 20 patients in 3 Wuhan hospitals; 10 treated with convalescent plasma (200ml with neutralizing antibody titer > 1:640) and 10 matched controls

- Study reports significantly improved clinical and radiographical markers with all 10 treated patients having de-escalation or cessation of respiratory support therapy.
- Cases were compared to a control group of 10 randomly selected patients from the same hospitals and matched by age, gender and disease severity.
- All patients also received maximal supportive therapy and antiviral therapies.
- Compared with the control group, the group treated with convalescent plasma had significantly higher oxygen saturation (median 93% vs 96%) and a higher number of improved/discharge patients. Due to the small sample, the differences were not statistically significant.
- There were no significant morbidities and mortalities associated with convalescent plasma.
- Limitations include use of concomitant therapies, lack of details regarding clinical outcomes, and the lack of power.

Finally, two news articles discussed individual critically ill patients (a 69 year-old female and 74 year-old female) from China who experienced clinical improvement after receiving convalescent plasma therapy.

Other viral illnesses

There is low-quality evidence, primarily observational/retrospective uncontrolled case series with small sample sizes reporting benefit for convalescent plasma use in severe viral respiratory illnesses. The

majority of the evidence is derived from treatment of SARS, with a two studies in H1N1 influenza. Some data suggests that early administration of convalescent plasma confers more benefit than delayed administration, possible due to suppression of viremia and avoidance of the immune hyper-activation. Overall, little meaningful conclusions can be drawn from these studies due to their limitations.

Soo et al 2004: A small retrospective cohort of convalesncent plasma compared to increased doses of corticosteroid for 40 patients infected with SARS who deteriorated despite ribavirin and lower-dose steroids showed that those who received convalescent plasma group had a lower chance of death (N=0 vs. 5, NS)

Cheng et al 2004: 80 patients with SARS who had deteriorated despite standard treatment which included antibiotics, ribavirin and corticosteroids were given convalescent plasma. The study found that the mortality rate in these patients was 12.5% compared to historically documented SARS mortality of 17% in Hong Kong. The study noted that administration of plasma earlier in disease course, particularly prior to day 14 had more impact in mortality vs. later administration (6.3% mortality vs. 21.9%).

Yeh et al 2005: Three health-care worker with SARS in China all received convalescent plasma and all survived. A similar 3-person case series of MERS patients by Ko et al, 2018, also administered convalescent plasma and reported treatment success.
Two studies by the same authors, Hung et al. of H1N1 patients comprise the most robust support for convalescent plasma; however must be interpreted with caution as generalizability to COVID-19 may be limited. In 2011, 93 pts w H1N1 who required ICU-level care, were given convalescent plasma vs. supportive care in a non-randomized fashion. Supportive care was not defined. Plasma group had lower mortality (20% vs 55%) which was stated to be statistically and clinically significant. A follow-up study two years later in 2013 with improved methodology was conducted. This multicenter prospective double-blind RCT evaluated IVIG donated by 2009 H1N1 survivors vs. IVIG from patients not previously infected. While viral load were lower in the treatment group, a subgroup analysis found a mortality benefit only for patients who received the IVIG with H1N1 antibodies within 5 days of symptom onset.

Summarizing data published on convalescent plasma for the treatment of MERS, two narrative reviews concluded that while studies are promising, no definitive recommendations can be made due to lack of properly conducted clinical trials (Mustafa et al 2018, Mo et al 2016). Another narrative review that combined 8 observational trials of SARS and H1N1 patients by Mair-Jenkins 2015 et al. showed improved mortality after convalescent plasma but is flawed by the low or very low quality of included studies and an inability to combine outcomes numerically.

There are several additional studies that are less relevant in this assessment, for example those evaluating treatment in conditions such as Ebola, rubella, hepatitis A and viral myocarditis which were not reviewed or considered.

In addition to the inherent risks associated with blood product utilization there are theoretical risks specific to convalescent plasma therapy. Antibody dependent enhancement (ADE) results in the enhancement of the target disease in the presence of the antibodies given. There is also the possibility of attenuation of the natural immune response. The most common side effects of treatment with convalescent plasma are minor transfusion related reactions (urticaria, febrile non-hemolytic transfusion reaction and pruritis). Reported rates for these minor complications range from 10-70%. One RCT investigating high vs. low-titre influenza plasma reported 34% of patients experiencing a serious adverse event including ARDS and respiratory distress.

Overall, convalescent plasma poses and attractive treatment option that warrants further investigation for the treatment of COVID-19. A careful consideration regarding the feasibility of large-scale treatment with blood products for this disease in conjunction with risks and costs needs to be undertaken.

Intravenous Immunoglobulin G (IVIG)

IVIG is pooled from human plasma of several thousand donors and used in the treatment of a large number of heterogeneous indications, including primary and secondary immune deficiency states and various autoimmune and inflammatory disorders. IVIG has several potential anti-inflammatory and immunomodulatory effects including provision of neutralizing antibodies to microbial toxins, altering

regulatory T-cells and affecting the complement system. In the field of infectious diseases, IVIG has been used as adjunct treatment to manage secondary complications of bacterial and viral illness, for example in treatment of neuroimmunologic disorders like Guillain-Barré syndrome or toxin-mediated shock.

Specific to COVID-19, various suggestions have been made that IVIG may play a role as salvage therapy for cytokine storm and related complications such as myocarditis. Thus far, while many commentaries exist, there are two case reports that describe the use of IVIG specifically for COVID-19.

Cao at al. 2020 published the first case series of three patients who were given salvage treatment for COVID-19 in Wuhan, China.

- Three patients who were deteriorating in hospital were given high dose IVIG (25g/day x 5 days).
- Average administration was 10 days after symptom onset.
- The case report states all patients improved clinically and radiographically 2-7 days later; however few specific details were given.
- Patients received concomitant therapy with antivirals, steroids and antibiotics.

Hu et al 2020 described a single patient who received IVIG for myocarditis caused by COVID-19.

- A 39-year-old male presented with an enlarged heart, pleural effusions and an elevated troponin and proBNP
- He received methylprednisolone and IVIG 20g/daily for 4 days, along with cardiac medications and antibiotics.
- The report stated that he improved within a week of admission.

Even though the evidence is limited, concerns have grown over the desire to use IVIG as a last resort therapy to those who are deteriorating. This is compounded by dwindling supply of IVIG during the pandemic, leading to a greater need to steward its use to those who have valid indications. The Canadian Blood Services issued a statement in early April that IVIG should be reserved for treatment of patients with approved indications rather than for experimental or salvage therapy of COVID-19.

Other Therapies

Tocilizumab –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 and Health Canada 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 peer-reviewed medical journal has published a case or case series as of March 30, 2020. In a small case series in Wuhan, China, published a non-peer reviewed Chinese website Chinaxiv.org, 20 critically-ill patients with elevated levels of IL-6 received tocilizumab. The document stated that 15 of the 20 patients (75.0%) had lowered their oxygen intake. The time frame of this change was not clear from the report. Biochemical markers such as the CRP and lymphocyte count improved in most patients. Due to the uncontrolled nature of the study, small patient numbers and lack of hard clinical outcomes, the efficacy of tocilizumab in the treatment of severe COVID-19 remains unknown (Xu 2020).

A second small case series from Bergamo, Italy published in a non-peer reviewed website medrxiv.org with 21 patients with pneumonia who developed pneumonia/ARDs but only required CPAP or non-invasive ventilation. The series was treated with siltuximab, a chimeric mAb that binds to and blocks IL-6. Biochemical markers like CRP improved in all patients. However, 7/21 (33%) had improvement of their condition, 9/21 (43%) remained the same and 5/21 (24%) worsened and required intubation. There is no comparison group in this series and follow-up was only available to day 7 after administration. The World Health Organization recently held an informal consultation on IL-6 blockade and stated that there is interest in pursuing anti-IL 6 therapies in the setting of a clinical trial but no recommendations can be currently made. One of the largest unknowns discussed among the medical community is how to select patients who may benefit from therapy and regarding the utility and feasibility of measuring IL-6 levels in infected patients.

The theory behind anit-IL 6 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 2020). There exist 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).

Oseltamivir - Neuraminidase inhibitors do not seem to have activity against COVID-19 (Tan et al 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.

Steroids - Steroid use outside of the Surviving Sepsis Campaign is not recommended. Steroids have not demonstrated benefit in prior SARS or MERS epidemics. Steroids may increase viral shedding (Lee 2004) and impair immune function. However, steroids may be used if there is another clear-cut indication (e.g. coronavirus plus asthma exacerbation, refractory septic shock). WHO guidelines for the supportive treatment of COVID-19 echo this statement. 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 conducted a comprehensive review and concluded that routine use of steroids solely for the indication of viral pneumonia cannot be supported.

Antibiotic Therapies

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. At Island Health, the 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 x1 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. At VIHA, piperacillin/tazobactam or a carbapenem is the standard of treatment, with added vancomycin if the patient has MRSA risk factors.

NSAIDs – On March 17, the World Health Organization recommended NSAIDs should be avoided for treatment of COVID-19 symptoms avoid taking ibuprofen, 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-I and ARBs – 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 various; 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.

Recommendations on April 2, 2020

IMAC recommends the following regarding therapies for COVID-19 and associated infections:

1. Lopinavir/ritonavir: We recommend against the routine use of lopinavir/ritonavir outside a randomized-controlled trial (e.g. CATCO).
2. Ribavirin and interferon: In light of insufficient evidence and potential adverse-effects, we advise against the use of ribavirin and interferon.
3. Remdesivir: While treatment with remdesivir remains promising, obtaining the drug for compassionate use does not produce the drug in a timely manner. We recommend against further attempts to obtain remdesivir. We recommend enrollment in a randomized-controlled trial of remdesivir if it becomes an option at VIHA.
4. Hydroxychloroquine/chloroquine: Based on the lack of clinically convincing outcomes, safety concerns and the fragility of the supply chain, we recommend against routine use of chloroquine or hydroxychloroquine. IMAC is committed to evaluating this particular therapy very closely. IMAC members are recommending a temporary restriction of the drug to ensure it is used for approved indications.
5. Toculizimab/Sarilumab: We were unable to evaluate any convincing evidence published in English that supports the use of tocilizumab. Although limited Chinese literature uses promising language, we currently cannot recommend routine its administration for COVID-19. We support the participation in a clinical trial if it becomes feasible.

6. Convalescent Plasma: The use of convalescent plasma warrants further study. We support the initiatives of the Canadian Blood Services in evaluating and operationalizing convalescent plasma therapy. We will evaluate trial opportunity on a case-by-case basis based on feasibility at VIHA.
7. Intravenous Immunoglobulin G: There is no evidence to support the use of intravenous immune globulin (IVIG) for the treatment of COVID-19 infection and it should not be used for this indication. It is critical to prioritize the use of IVIG for patients with established clinical indications to preserve the adequacy of its supply.
8. Other agents: We recommend against treatment with any other investigational agent, including ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab and thymosin due to lack of data, lack of availability, or both.
9. We acknowledge that there will be some patients in whom salvage efforts may be appropriate. We leave those decisions to individual prescribers and encourage them to contact Infectious Disease Specialists, Medical Microbiologists and/or ID&AMS pharmacist for discussion about appropriateness, safety and operational details.
10. IMAC supports practicing evidence-based medicine and recommends against exceptionalism. We encourage clinicians to obtain best-practice information from reputable sources such as medical literature of acceptable quality, World Health Organization, BC Center for Disease Control and not from blogs, news articles, press interviews, social media and politicians.
11. We recommend that VIHA become a partner site for any randomized controlled trials (e.g. CATCO) that would allow ethical and appropriate evaluation of investigational use of therapies. This option is also favourable as it would not deplete the sensitive supply chain of drugs for those who require it for approved indications.
12. We recommend against the use of natural health products or Chinese medicines for treating COVID-19 due to lack of data or an inability to evaluate the data in English.
13. We recommend against the use of oseltamivir outside its current indication for suspected and confirmed influenza.
14. We recommend that patients with suspected or confirmed COVID-19 who meet diagnostic criteria for CAP be started on ceftriaxone and azithromycin for concomitant bacterial infection until such infection is ruled out.

15. We recommend against broad-spectrum antibiotic treatments based on travel history alone and reserve these agents for patients with significant risk factors for drug-resistant bacteria (e.g. exposure to health-care in an endemic area). Infectious Diseases Specialists should be consulted in these circumstances.
16. We recommend standard therapy of piperacillin/tazobactam or a carbapenem with or without vancomycin for the treatment of health-care associated infection such as hospital or ventilator associated pneumonia.
17. We recommend that patients on ACE-I and ARBs continue these agents as indicated and not cease therapy solely on the basis of COVID-19.
18. We recommend that acetaminophen be used preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.
19. We recommend that the summary articulating these points be posted on the VIHA COVID-19 website, the Medical Affairs website and circulated internally as a reference for best practices. Evidence would be reviewed regularly by IMAC and this reference would be regularly updated. We have published a concordant SPECTRUM pathway and recommend that it is promoted.

Search Terms: ("COVID-19"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND 2019/12[PDAT] : 2030[PDAT])) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
Search Databases: PubMed, Medline, Ovid
Search Date: March 19, 2020

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