Clinical Reference Group SBAR: Therapies for COVID-19

UPDATED: May 18th, 2020

The British Columbia COVID-19 Therapeutics Committee (CTC) meets weekly to discuss the most current research on the use of therapies in the management of COVID-19.

Situation

SARS-CoV-2 (previously named 2019-nCoV), the virus that causes the clinical illness COVID-19, is a novel RNA virus belonging to the coronavirus family. With over four million 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 Therapeutics 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, Long Term Care and Pharmacy. The COVID Therapeutics Committee has also provided general treatment guidelines for anti-infective use in the setting of viral pneumonia for in-patients. As this is an evolving situation, we are making the necessary amendments to this SBAR along with up-to-date recommendations weekly, and as emerging information becomes available.

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 have suggested 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: 1. lopinavir/ritonavir (Kaletra®), an anti-retroviral used for treatment of HIV; 2. remdesivir, a novel investigational antiviral; and 3. hydroxychloroquine, an antimalarial drug with antiviral activity *in-vitro*. Other agents also under investigation including immunomodulatory agents used to attenuate COVID-19-associated cytokine storm such as tocilizumab and sarilumab. As of May 16, 2020, the Cochrane COVID-19 Study Register lists 1598 interventional studies of which 1039 are randomised trials. *In-vitro* data and animal studies of various agents, mainly for the treatment of SARS-CoV-1, 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 hundreds of publications. The following pharmaceutical agents are discussed in detail below (see "Assessment"):

1. lopinavir/ritonavir[#] (Kaletra®)
2. remdesivir[#]
3. chloroquine or hydroxychloroquine[#]
4. oseltamivir
5. ribavirin and interferon
6. colchicine[#]
7. ascorbic acid
8. tocilizumab or sarilumab[#]
9. convalescent plasma[#]
10. intravenous immunoglobulin (IVIG)
11. corticosteroids
12. antibiotics

[#] Denotes that a clinical trial of named therapy is currently planned or underway in British Columbia. Links below for registered trials in Canada and British Columbia.

Canada:
https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-clinical-trials/list-authorized-trials.html

British Columbia:
https://bcahsn.ca/covid-19-response/inventory/

Articles commenting on safety of other agents, for example Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs), and Venous Thromboembolism (VTE) prophylaxis in the context of COVID-19 have also been published. These topics are also discussed in detail below (see "Assessment").

Other investigational therapies that have been suggested by various medical and non-medical literature sources include ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab, ivermectin, niacin, thymosin, natural health products, and traditional Chinese medicines. Information on these therapies are limited due to lack of data, lack of availability, or both. Detailed assessment on these therapies will be provided when credible scientific literature becomes available.

Expert bodies such as the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Public Health Agency of Canada (PHAC), the Surviving Sepsis Campaign (SSC) (a joint initiative of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)), the Australian and New Zealand Intensive Care Society (ANZICS), the Canadian Critical Care Society (CCCS), the Association of Medical Microbiology and Infectious Disease Canada (AMMI), and the Infectious Diseases Society of America (IDSA) have made

recommendations for treatment of COVID-19 but they are limited to supportive care. All support the enrollment of patients in clinical trials for currently unproven therapies. The WHO published 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."*

It is recognized that there may be extenuating clinical circumstances where clinicians decide to use unproven therapies when clinical trials are unavailable. In those circumstances **where unproven therapies are used, the WHO has provided a standardized case report form for data collection to ensure that there is contribution to scientific research and the clinical community.**

Locally, in British Columbia, there is consensus between expert 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 agreement is that investigational treatments will not be used outside of approved randomized controlled trials (RCTs). This also applies to specific patients like those with immunocompromising conditions (e.g. solid organ transplant). Many BC Health Authorities have committed to enrolling in RCTs such as the CATCO study which aims to investigate the use of lopinavir/ritonavir (Kaletra®) in the treatment of COVID-19 in hospitalized patients. This RCT is led by Dr. Srinivas Murthy (Infectious Diseases and Critical Care) from BC Children's Hospital and funded through the Canadian Institutes of Health Research. Another study is planned to investigate sarilumab in COVID-19 patients at Vancouver General Hospital under the supervision of Dr. Ted Steiner (Infectious Diseases).

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 hydroxychloroquine prophylaxis in healthcare workers and contacts, use of convalescent plasma in infected patients, and use of colchicine in infected out-patients. The BC Health Authorities are currently reviewing the local feasibility of these clinical studies on a daily basis.

Assessment

Lopinavir/Ritonavir (Kaletra®)
Recommendation: Recommend against the 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.

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.
- An interim analysis showed that the trial was underpowered, however, enrollment was suspended as remdesivir became available.

Li 2020: ELACOI partially blinded randomized controlled trial of 86 patients with mild to moderate clinical status with confirmed SARS-CoV2 PCR in Guangzhou, China. Currently only available as non-peer reviewed pre-print.
- 34 patients were randomized to receive lopinavir/ritonavir 400/100 mg PO BID for 7-14 days, 35 patients to arbidol 200 mg PO TID for 7-14 days, and 17 patients received no antiviral therapy. Therapy was discontinued after 7 days if patients had 2 pharyngeal swabs negative for SARS CoV2 separated by 24 hours, on hospital discharge or had intolerable side effects from antiviral therapy. Median age 49, no significant differences in baseline characteristics, although numerically higher number of patients received corticosteroids in the lopinavir/ritonavir arm.
- Patients, physicians and radiologists that reviewed data and radiologic images were blinded to treatment allocation but open-label to clinicians that recruited patients and research staff.
- Primary outcome=time of positive-negative conversion of SARS-CoV2 nucleic acid from treatment initiation to day 21. Nine days with lopinavir/ritonavir vs 9.1 days with arbidol vs 9.3 days with standard care.
- 35.3% of lopinavir/ritonavir patients experienced adverse effects (primarily GI), one patient required discontinuation of therapy. Eight patients on lopinavir vs 3 patients on arbidol vs 2 patients on standard care progressed to severe/critical clinical status.
- Planned enrollment of 125 patients but did not achieve this due to low numbers of new COVID-19 patients

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 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 lopinavir/ritonavir.

Remdesivir
Recommendation: Recommend against the 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).

Remdesivir is currently not available for commercial use within Canada. It was previously available as compassionate use via Health Canada's Special Access Program for individual case-by-case applications. However, this process has since been halted as Gilead transitioned to provision of access through clinical trials. Exceptions are currently being made for pregnant women and children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.

With the press release statement of positive results from the NIAID clinical trial of remdesivir, the current status of ongoing clinical trials that are either studying remdesivir or planning to add remdesivir as a treatment group are under evaluation.

As of May 16, 2020, there have been at least one published RCT, one published case series, and a preliminary press release by the NIAID of the NIH releasing details of their own sponsored study. In response to the positive preliminary results of the NIAID clinical trial, on May 1, 2020, the FDA issued an Emergency Use Authorization of remdesivir. This is the third time the FDA has issued such a release for a pharmacologic therapy.

On May 12, 2020, based on preliminary results from their own sponsored study, the NIH recommends remdesivir for treatment of COVID-19 in hospitalized patients with severe disease defined as SpO2 below 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. The NIH does not recommend remdesivir for mild to moderate COVID-19. The NIH also notes that remdesivir is not FDA approved. At this time, in the absence of a full peer-reviewed publication of the NIH study and the publication of a smaller Chinese RCT with negative findings for remdesivir, the BC COVID-19 Therapeutics Committee recommends against use of remdesivir outside of randomized controlled trials. Remdesivir is not readily available in Canada.

Human Data

NIAID NIH 2020-04-29
- A news statement released by the NIAID of the NIH shared preliminary results of the ACTT trial (ClinicalTrials.gov NCT04280705)
- randomized, double-blinded, placebo-controlled trial in 1063 hospitalized patients with "advanced COVID-19 and lung involvement" compared remdesivir versus placebo
- trial started recruitment February 21, 2020 and included 68 sites across USA, Denmark, Germany, Greece, Spain, United Kingdom, South Korea,, Singapore, Mexico
- included hospitalized adult patients with lab confirmed COVID-19 and at least one of the following: pulmonary infiltrates on radiographic imaging, SpO2 below 94% on room air, requiring supplemental oxygen, or on mechanical ventilation; excluded those with ALT/AST 5 times above ULN, GFR below 30, or pregnant/breastfeeding
- full data not yet released, preliminary release states that patients treated with remdesivir recovered faster than those on who received placebo (11 days vs 15 days p<0.001); recovery

was defined as first day on which the patient no longer requires supplemental oxygen or ongoing medical care
- statistically non-significant trend in reduced mortality in favour of remdesivir (8.0% vs 11.6%, p=0.059)
- full trial details are awaiting peer-reviewed publication

Wang 2020-04-29
- randomized, double-blinded, placebo-controlled trial of 237 patients in 10 hospital sites in Hubei, China from February 6 to March 12, 2020
- included participants age over 18, confirmed SARS-CoV-2, positive chest imaging for pneumonia, oxygen saturations below 94% on room air or PaO2 to FiO2 ratio below 300, and within 12 days of symptom onset; excluded participants who were pregnant, cirrhosis, ALT or AST above 5 times upper limit of normal, GFR below 30 or on dialysis
- randomized 2:1 to remdesivir 200 mg IV x 1 day, then 100 mg IV daily x 9 days versus placebo
- terminated early due to inability to recruit with control of local outbreak in Wuhan
- underpowered based on the original sample size calculation of 453
- at baseline, more patients in the remdesivir group had hypertension, diabetes, and coronary artery disease; other baseline characteristics were similar; admission NEWS 2 score was 4 to 5; median age 65 and about 60% male
- median time from symptom onset to study treatment was 11 vs 10 days
- during the trial, the following concomitant medications were permitted in each group: interferon IV (29% vs 38%), lopinavir/ritonavir (28% vs 29%), antibiotics (90% vs 94%), corticosteroids (65% vs 68%)
- primary endpoint was time to clinical improvement within 28 days defined as a change in 6-point ordinal scale by 2 points or discharge from hospital; there was no difference in primary endpoint (21 vs 23 days, HR 1.23 [95%CI 0.87 to 1.75])
- numerically faster improvement in primary outcome with remdesivir in subgroup with symptom onset less than 10 days (18 vs 23 days, HR 1.52 [95%CI 0.95 to 2.43])
- no significant differences in mortality at 28-days (14% vs 13%, difference 1.1% [95%CI -8.1 to 10.3])
- there were no consistent effects on viral load between groups from day 1 to 28
- serious adverse events were less common in remdesivir (18%) vs placebo (26%); common adverse events (>10%) that occurred more in remdesivir group included thrombocytopenia and hyperbilirubinemia
- overall, clinical conclusions from this RCT are limited due to its premature termination, relatively prolonged duration from symptom onset to treatment, and concomitant anti-viral medication use; there were no apparent differences in time to clinical improvement, mortality, or rate of viral clearance between remdesivir and placebo in this study

Grein 2020-04-20
- Case series 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-day course of remdesivir if they had oxygen saturation of 94% or less while on room air or 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.

Holshue 2020-01-31

- Single case report of a patient who 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.

Chloroquine and Hydroxychloroquine

Recommendation: Recommend against the use of chloroquine and hydroxychloroquine for treatment or prophylaxis outside a randomized-controlled 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 and 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 interfering with virus trafficking within cells, and immunomodulatory effects which may attenuate cytokine storm reactions in severe disease. However, it should be noted that immunomodulatory effects may be harmful in viral disease.
There is currently a drug shortage of chloroquine in Canada. Hydroxychloroquine is available in Canada and is on the BC provincial formulary. However, due to strong global demand of hydroxychloroquine supplies of hydroxychloroquine are unstable.

The safety of hydroxychloroquine has not been assessed in robust clinical studies in the treatment of coronavirus infections. Recently, one death and one hospitalization occurred in Arizona after a couple took a single dose of veterinary-grade chloroquine for prophylaxis. Numerous overdoses have also been reported in Africa, where both drugs are used for malaria prophylaxis. However, if used under medical supervision, hydroxychloroquine is well tolerated based on experience in patients with rheumatoid arthritis. Common side effects include gastrointestinal intolerance. Less common side effects 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.

Various clinical trials of hydroxychloroquine have recently been registered. As of May 14, 2020, the Cochrane COVID-19 Study Register lists 246 randomized interventional studies with reference to chloroquine or hydroxychloroquine as one of the study groups.

Human Data
As of May 14, 2020, there are at least 17 published human studies that describe the effects of chloroquine or hydroxychloroquine in COVID-19. In general, the methodological quality of these studies

is poor. Five of the studies are randomized controlled trials; three are observational cohort studies with propensity matching; four are observational cohort studies with no methods employed to match controls; and five are case series with no control arm. Of the five randomized studies, three are published in non-peer reviewed manuscript databases, one is published in an editorial format, and one is published primarily in Chinese language with an English language abstract. Published studies that do not undergo rigorous independent peer-review may be susceptible to an over-exaggeration of clinical benefits and an underreporting of potential harms. Common methodological shortcomings of the five published randomized trials to date include small sample sizes, unclear rationale for inclusion and exclusion criteria, lack of placebo control arm, lack of clinically meaningful objective outcomes, and premature study termination. Due to these limitations, published literature to date, both individually and collectively, provide insufficient data to recommend chloroquine or hydroxychloroquine as treatment options for COVID-19 and there are weak signals of potential adverse effects.

Rosenberg (2020-05-11)
- observational cohort multicenter study of 1438 patients at 25 New York City hospitals
- Cox-proportional hazard model used for adjusting primary outcome of in-hospital mortality found no differences comparing hydroxychloroquine versus standard of care (aHR 1.08, 95% CI 0.63 to 1.85) nor hydroxychloroquine and azithromycin versus standard of care (aHR 1.35, 95% CI 0.76 to 2.40)
- secondary outcomes found more cardiac arrests with hydroxychloroquine and azithromycin versus standard of care (OR 2.13, 95% CI 1.12 to 4.05) and no differences with QTc prolongation
- large observational study limited by its non-randomized nature; despite adjustment of primary outcome based on covariates, this does not address known and unknown sources of confounding; a low certainty signal of cardiovascular harm was found with combination hydroxychloroquine and azithromycin

Geleris 2020-05-07
- observational cohort study with propensity score matching of 1376 patients in New York using a database that compared patients who received hydroxychloroquine with or without azithromycin matched to those who did not (peer reviewed publication)
- primary outcome of intubation or death in the primary analysis with propensity score matching and adjustments showed no differences between treatment and controls (HR 1.04, 95% CI 0.82 to 1.32)
- limitations include its non-randomized nature which does not control for all known and unknown confounders and biases; also, as this was a database study, confirmation of medication regimens and doses received was not performed
- this large study suggests there are no differences in outcomes in those who receive hydroxychloroquine with or without azithromycin compared to controls; however, RCT evidence is needed to confirm findings

Huang 2020-05-04:
- observational cohort study of 373 patients from 12 hospitals in Guangdong and Hubei, China (non-peer reviewed publication)
- compared hospitalized patients with "moderate" severity illness who received chloroquine up to 10 days versus standard of care

- patients presented between 2 to 25 days of symptom onset and no patients required transfer to ICU or died
- primary outcome was time to viral clearance per RT-RNA test which favored chloroquine (3 vs 9 days, difference 6 days, p < 0.0001)
- no differences in duration of hospitalization or no meaningful differences in duration of fever
- study is severely limited by its observational nature and lack of generalizability to hospitalized patients in BC as none of the 373 patients required transfer to ICU and there was a very wide range of duration of symptom onset to treatment

Mercuro 2020-05-01:
- observational case series of 90 patients from Boston assessing QTc effects of hydroxychloroquine with or without azithromycin (peer reviewed publication)
- QTc above 500 msec in hydroxychloroquine only group was 7/37 (19%) whereas in combination group was 11/53 (21%)
- 1 case of documented torsades in a patient taking hydroxychloroquine and azithromycin (QTc 499)
- study is limited by its lack of control group and relatively small numbers

Bessiere 2020-05-01:
- observational case series of 40 patients from a French ICU that assessed QTc effects of hydroxychloroquine with or without azithromycin (peer reviewed publication)
- for all patients, found QTc prolongation above 500 msec in 7/40 (18%) participants with more QTc prolongation in the combination therapy group 6/18 (33%) than the hydroxychloroquine group alone 1/22 (4.5%); no reported episodes of ventricular arrhythmias or torsades
- study is limited by its lack of control group and relatively small numbers

Yu 2020-05-01:
- observational cohort study of 568 critically ill patients from Wuhan, China to assess hydroxychloroquine versus standard of care (non-peer reviewed publication)
- hydroxychloroquine group only had 48 patients; concomitant medications given to patients included lopinavir/ritonavir or ribavirin (44%), IVIG (50%), and "immunoenhancers" (17%)
- study found lower mortality rates with hydroxychloroquine 9/48 (19%) versus standard of care 238/520 (46%) and more effects on lowering IL-6 levels in the hydroxychloroquine group
- study is limited by its observational nature with threats to selection, performance, and detection bias as well as markedly small numbers in the hydroxychloroquine group; in addition, due to the various concomitant therapies employed in this study, it is difficult to generalize to North American patients

Magagnoli 2020-04-23:
- observational cohort study with propensity score matching of 368 male patients from United States Veterans Health Administration in Virginia (non-peer reviewed publication)
- selected hospitalized patients with confirmed SARS-CoV-2 infection and identified patients based on bar code medication administration data
- compared hydroxychloroquine (n=97) vs hydroxychloroquine and azithromycin (n=113) vs standard of care (n=158) [doses and durations of therapy not reported]
- patients were matched on various co-variables including age, sex, race, BMI, comorbidities, vital signs, lab data

- deaths were more common in hydroxychloroquine group vs standard of care group, 27.8% vs 11.4% (aHR 2.61, 1.10 to 6.17); no significant differences with hydroxychloroquine and azithromycin group
- there were no differences in need for mechanical ventilation
- this trial has numerous limitations including its non-randomized nature (selection bias) and the fact that patients were identified in this database study based on drug dispensing via barcode system where no details regarding drug doses, duration, or relative start dates are known; additionally, despite efforts to balance groups using propensity score matching, risk of confounding by indication and residual confounding in studies with this type of design cannot be excluded
- results from this study should be regarded as hypothesis generating; randomized controlled trials are still required to investigate the true benefits vs harms of hydroxychloroquine in COVID-19

Tang 2020-04-14 & Tang 2020-05-14:
- randomized, open-label multi-center study at 16 hospital sites with 150 patients in China (initial non-peer reviewed publication in medrxiv then later published in BMJ)
- 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" as per medrxiv publication. 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)
- in the BMJ publication, early trial termination was decided due to low recruitment numbers with no mention of the above post-hoc subgroup analysis
- 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 late presentation and mild COVID-19 disease

Mahevas 2020-04-14 & Mahevas 2020-05-14:
- observational cohort study with propensity score matching at four hospitals with 181 patients in France (non-peer reviewed publication in medrxiv, then later published in BMJ)

- included hospitalized patients on general medical wards requiring oxygen by nasal prongs or face mask
- compared hydroxychloroquine 600 mg daily within 48 hours admission (n=84) vs usual care (n=89) and matched patients using 15/19 variables such as age, gender, comorbidities, immunosuppressants, and physiologic variables
- no differences found in primary outcome of survival without transfer to ICU at day 21: HCQ 76% vs SoC 75% (aHR 0.9, 95% CI 0.4 to 2.1)
- also no differences overall survival at day 21 nor survival without ARDS at day 21
- ECG changes in hydroxychloroquine group 8/84 (9.5%) that required treatment discontinuation after 4 days
- study was a well-performed relatively small observational study with adequate matching of patients and measures were taken to minimize the effects of known confounders and time-dependent bias; no significant differences were in efficacy outcomes were demonstrated in this study and a low certainty signal of increased risk of ECG changes with hydroxychloroquine was found

Borba 2020-04-11:
- randomized, double-blinded single-center clinical trial of 81 hospitalized patients enrolled in Brazil; CLORO-COVID study; preliminary safety results (initial medrxiv publication, then published in JAMA Network Open)
- compared chloroquine base high dose 600 mg twice daily x 10 days (n=41) vs chloroquine base low dose 450 mg twice daily x 1 day, then 450 mg daily x 4 days, then placebo to complete 10 days (n=40); all patients received ceftriaxone x 7 days and azithromycin 500 mg daily x 5 days
- a complete placebo arm was not studied as the investigators reported it was "unethical" to evaluate chloroquine vs placebo as per Brazil's national regulatory health agencies
- preliminary results evaluated outcomes at day 6 (full study to look at day 28)
  - high dose chloroquine arm was associated with trends towards higher mortality: 7/41 (17%) vs 4/40 (10%)
  - high dose arm also associated with increased incidence of QT prolongation above 500 ms: 7/28 (25%) vs 3/28 (11%)
  - no differences in viral negativity rate at day 5: 1/12 (8.3%) vs 0/14 (0%)
  - the high dose arm is no longer recruiting due to signal of harm
- limitations of this study include lack of placebo group to discern true benefits vs harms of any dose of chloroquine, the small sample size of this preliminary study, and the truncated study results at day 6; due to these concerns, results should be interpreted with an abundance of caution
- this study adds very little to our current knowledge of benefits vs harms of chloroquine in treatment of COVID-19

Chorin 2020-04-03:
- observational case series 84 hospitalized patients in New York taking hydroxychloroquine and azithromycin for COVID-19 to assess effects on QTc (non-peer reviewed publication)
- average ECG follow-up from exposure was 4 days
- average QTc prolonged from 435 (24) ms to 463 (32) ms at day 4, p < 0.001
- 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.

Huang 2020-04-01:
- randomized, open label, study of 22 hospitalized participants in Guangdong, China; published (peer-reviewed but trial registration not reported)
- 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
- 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 2020-03-30:
- observational 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
- mean blood trough hydroxychloroquine concentration 678 mg/L (range 381 to 891)
- 8/10 patients still tested positive in nasopharyngeal swabs at days 5 to 6 after treatment
- limitations of this study include its very very small small sample size and its lack of control group
- difficult to draw any meaningful conclusions besides to note that the viral PCR effect of hydroxychloroquine plus azithromycin in this small group of patients was not nearly as evident as the original Gautret study listed below

Chen 2020-03-30:
- randomized, open label, single-center clinical trial in Wuhan, China (non-peer reviewed publication but registered 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
- time to cough resolution was faster in hydroxychloroquine group (2.0 vs 3.1 days); however, only 71% and 49% of respective groups had cough on day 0
- 4 patients in the control group "progressed to severe illness"; this was not well defined
- 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 2020-03-28:
- observational case series of 80 hospitalized patients in a single-center in France
- 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
- 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.
- 93% of participants had negative viral PCR at day 8; viral cultures done in select patients were 97.5% negative by day 5
- at time of writing, 1/80 patients died, 14/80 patients still hospitalized (3/80 patients admitted to ICU), and 65/80 patients discharged home
- 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 2020-03-24:
- randomized open-label single center pilot study; Shanghai China university journal; English abstract only; full article in Chinese; registered trial NCT04261517
- 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 and no difference was observed between groups (hydroxychloroquine 13/15 (86.7%) vs usual care 14/15 (93%), p > 0.05)
- 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 2020-03-20:
- observational cohort series of 42 hospitalized patients in France with positive viral study (initial medrxiv publication, then published in International Journal of Antimicrobial Agents; however, in the peer-reviewed publication, one of the authors of this study is the Editor-in-Chief of the publication journal; the professional society of this journal (ISAC) and Elsevier issued a statement on Apr 11th, 2020 that an independent peer-review of this study is ongoing)
- 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

- 6 patients in the study were asymptomatic throughout the study
- study primary endpoint 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
- 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
- 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

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 2020). No clinical evidence was provided to support this recommendation.

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 EC_{50} 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 EC_{50} 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 routine use of oseltamivir unless suspected or confirmed influenza infection.

Neuraminidase inhibitors do not appear 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 limited clinical trials evaluating the efficacy and safety of ribavirin and/or interferon in combination with other therapeutic agents for COVID-19 treatment.

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.

(Wan et al. 2020) studied a total of 135 hospitalized patients with COVID-19. All patients received antiviral therapy (135 [100%] (Kaletra and interferon were both used), antibacterial therapy (59 [43.7%]), and corticosteroids (36 [26.7%]). In addition, many patients received traditional Chinese medicine (124 [91.8%]). It is suggested that patients should receive Kaletra early and should be treated by a combination of western and Chinese medicine. As of February 8, 2020, a total of 120 patients remained hospitalized, 15 patients (11.1%) were discharged, and one patient had died. The 28-day mortality rate was 2.5%. It is unclear of the role of interferon in this combination regimen.

(Yuan et al., 2020) evaluated viral clearance and biochemical markers (IL-6 and CRP) of 94 discharged COVID-19 patients. Interferon + lopinavir/ritonavir (N=46) and *interferon-alpha* + lopinavir/ritonavir + *ribavirin* (N=21) appeared beneficial, and LDH or CK reductions appeared to be associated with favourable outcome. Doses and regimens were not indicated. Both regimens appeared beneficial with no differences in length of stay or PCR negative conversion. The role of interferon is unclear as other antivirals were used in both treatment arms.

(Qui et al, 2020) retrospectively reviewed epidemiological and clinical data of confirmed COVID-19 pediatric patients (aged 0-16 years; mean 8.3 years) from 3 hospitals in Zhejian, China. All 36 children received *interferon alfa* by aersolization BID, 14 (39%) Kaletra syrup BID, and 6 (17%) required O2. All patients were cured. The role of interferon is unclear as Kaletra was also used.

(Hung et al, 2020), conducted a multi-centre, prospective, open-label, randomized, Phase 2 trial in mild to moderate COVID-19 patients in Hong Kong. Patients received a combination of lopinavir 400 mg/ritonavir 100 mg every 12 hours, ribavirin 400 mg every 12 hours, and interferon beta-1b 8 million international units subcutaneously on alternate days (n=86) vs. lopinavir 400 mg/ritonavir 100 mg every 12 hours for 14 days (n=41) control. Median time from start of treatment to negative nasopharyngeal swab was shorter in the combination group (7 days vs. 12 days, harard ratio 4.37 [95% CI 1.86 to 10.24], p=0.0010). Median time from start of study to treatment was 5 days. Limitations included open-label design and 34 patients in the combination arm did not receive interferon as they were admitted 7 days

after symptom onset and the median number of interferon doses was 2. Based on this study, we are unable to conclude the benefit of the individual agents.

In vitro Data
Data from a molecular docking experiment using the SARS-CoV-2 RNA dependent RNA polymerase (RdRp) model identified tight binding of sofosbuvir and ribavirin to the coronavirus RdRp, thereby suggesting possible efficacy of sofosbuvir and ribavirin in treating the COVID-19 infection (Elfiky 2020).

Interferons have also been shown to suppress the viral replication of SARS in vitro and been considered for the current outbreak in China (Chan et al. 2020).

Interferon-alpha and beta at 50 IU/mL reduces SARS-CoV-2 titres by 3.4 log and 4 log in Vero cells, respectively. EC50 of interferon-alpha and beta is 1.35 IU/mL and 0.76 IU/mL, respectively. Interferon appears to suppress SARS-CoV-2 replication *in-vitro*, corresponding to clinically achievable concentrations. (Mantlo et al. 2020)

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.

Colchicine
Recommendation: Recommend against the use of colchicine for treatment or prophylaxis outside a randomized-controlled trial.

Human Data:
Case series of two COVID-19 positive kidney transplant patients, with one being treated with colchicine. A 52-year-old female, 8 months post-transplant, was admitted to hospital and received colchicine 1 mg on Day 8, and 0.5 mg/day thereafter, as well as concurrent hydroxychloroquine 200 mg orally twice daily, antivirals (darunavir plus cobicistat) and antibiotics. Interleukin-6 concentration decreased to 36 pg/mL after 24 hours, and patient appeared clinically stable on Day 14 (at time of publication). No conclusive recommendations can be drawn from the treatment of one transplant patient with concomitant therapies (Ganolfini et al 2020).

Retrospective study in Israel using a database to examine protective effects of hydroxychloroquine and colchicine against COVID-19, comparing those who tested positive vs. negative in terms of rate of administration of medications. Sample of 14,520 subjects were screened for COVID and 1317 were positive. No significant differences in rates of hydroxychloroquine or colchicine use between COVID-19 positive and negative patients (hydroxychloroquine 0.23% vs. 0.25% and colchicine 0.53% vs. 0.48%, respectively). Hydroxycholoroquine and colchicine do not appear protective for COVID-19. (Gendelman et al, 2020)

There are several ongoing clinical trials, based on the potential anti-inflammatory effects of colchicine.

(NCT04322682) The Montreal Heart Institute COLCORONA Study is a phase 3 multi-centre, randomized, double-blind, placebo-controlled outpatient study (n=6000) to determine the efficacy and safety of colchicine 0.5 mg PO bid x 3 days, then 0.5 mg daily x 27 days vs. placebo for treatment of COVID-19 infection in reducing death and lung complications.

(NCT04326790) Deftereos 2020 is conducting a prospective, randomized, open labelled, controlled study (n=180) in Greece comparing usual medical treatment and colchicine 1.5 mg PO x 1 (1 mg PO x 1 if receiving azithromycin), followed 60 min by 0.5 mg if no gastrointestinal effects), then 0.5 mg PO BID for weight >60 kg [0.5 mg PO daily if <60 kg] vs. usual medical treatment. The endpoints are time for CRP levels to be >3xUNL, difference in troponin within 10 days, and time to clinical deterioration.

(NCT04322565) An Italian phase 2 randomized, open-label study(n=100) evaluating colchicine 1 mg (or 0.5 mg in chronic kidney disease)/day and standard of care vs. only standard of care in mild and moderately ill COVID-19 positive patients with the endpoints of time to clinical improvement or hospital discharge.

(NCT04328480) This is an Argentinian phase 3 randomized, open-label, controlled trial (n=2500) assessing colchicine arm [colchicine 1.5 mg, then 0.4 mg after 2 hours, followed by 0.5 mg PO BID x 14 days or until discharge; if patient is receiving lopinavir/ritonavir, colchicine 0.5 mg, then after 72 hours 0.5 mg PO q72 hours x 14 days or until discharge; if patient is starting on lopinavir/ritonavir, colchicine 0.5 mg 72 hours after starting Kaletra, then 0.5 mg PO q72 hours x 14 days or until discharge] vs. standard of care in moderate/high-risk COVID-19 patients. The primary endpoint is all-cause mortality.

(NCT04350320) Spain - Phase 3, randomized, controlled, open-label trial comparing colchicine 1.5 mg , then 0.5 mg every 12 hours for 7 days, and 0.5 mg every 24 hours until completion of 28 days of total treatment) vs. standard of care in hospitalized COVID-19 patients within 48 hours (n=102). Primary endpoints are improvement in clinical status and IL-6 levels up to 28 days.

(NCT04360980) Iran - Randomized, double-blind trial evaluating colchicine 1.5 mg, then 0.5 mg BID and standard therapy vs. standard therapy (vitamin C 3 g daily , thiamine 400 mg daily, selenium, Omega-3 500 mg daily, vitamin A, vitamin D, azithromycin, ceftriaxone, Kaletra 400 BID for 10 days(n=80). Primary endpoints are clinical, virological, and biomarker resolution.

(NCT04355143) Los Angeles - Open-label, randomized trial of colchicine to reduce myocardial injury in COVID-19 (COLHEART-19) evaluating colchicine 0.6 mg BID x 30 days vs. standard of care (n=150). Primary endpoint is maximum troponin level at 30 days.

In vitro data:
SARS-CoV-2 proteins such as viroporins E, 3a and 8A involved in viral replication appear to activate NLRP3 (Castaño-Rodriguez 2018). Inflammasome NLRP3 is involved in innate immunity and is a proposed to be a major pathophysiological component in the clinical course of patients with COVID-19 (Deftereos 2020).

Ascorbic Acid

Recommendation: Recommend against the use of ascorbic acid for treatment or prophylaxis outside a randomized-controlled trial.

Ascorbic acid is an antioxidant and cofactor in a number of physiologic pathways including phagocytosis and chemotaxis of leukocytes, replication of viruses, and production of interferon. Animal studies have shown reduction of incidence and severity of bacterial and viral infections.

In vitro **data:** No studies were found specific to COVID-19, SARS or MERS

Human data:
- ARDS: CITRIS ALI Multicentre, double-blind, placebo-controlled RCT, 50 mg/kg IV q6h x 96 hrs did not significantly improve mSOFA scores at 96 hours or CRP/thrombomodulin levels at 168 hours. Forty-six prespecified secondary outcomes including mortality but no adjustments made for multiple analyses. No unexpected study-related adverse effects occurred.
- Septic shock: VITAMINS Multicentre, open-label RCT comparing ascorbic acid 1.5 g IV q6h PLUS thiamine 200 mg IV q12h PLUS hydrocortisone 50 mg IV q6h vs hydrocortisone alone until resolution of shock or up to 10 days. No statistically significant difference in outcome of time alive or vasopressor free up to 10 days. No serious adverse effects were reported.
- Common cold: Cochrane Systematic Review did not find that regular supplementation reduced the incidence of the common cold. No consistent effect in reduction of duration or severity of symptoms was seen in therapeutic trials.
- COVID-19: No studies of ascorbic acid in COVID-19 have been published to date but studies are ongoing.
  - NCT04264533 Blinded, placebo-controlled RCT in Zhongnan Hospital, China using ascorbic acid 12g IV q12h x 7 days versus sterile water in adults admitted to ICU with severe/critical SARI due to COVID-19. Primary outcome: ventilator free days at day 28. Study estimated to be completed by September 30, 2020.
  - NCT04323514 Open-label, longitudinal, non-comparator study in Palermo, Italy. Adults and children hospitalized with COVID-19 pneumonia will receive ascorbic acid 10 g IV once. Primary outcome of in-hospital mortality at 72 hours. Study estimated to be completed by March 31, 2021.
  - NCT03680274 LOVIT Multicentre blinded, placebo-controlled RCT in Canada comparing ascorbic acid 50 mg/kg IV q6h vs NS or D5W IV q6h x 96 hours in adult patients admitted to the ICU with suspected/proven infection (including COVID-19) on vasopressors. Primary outcome of death and persistent organ dysfunction. Study estimated to be completed by December 2022.
  - NCT04344184 EVICT-CORONA-ALI Blinded, placebo-controlled RCT in US comparing ascorbic acid 100 mg/kg IV q8h vs D5W IV q8h for up to 72 hours in adults hospitalized with PCR confirmed COVID-19 requiring oxygen supplementation or oxygen saturation of <93%. Primary outcome is number of mechanical ventilator-free days at day 28. Study estimated to be completed by May 2021
  - NCT04357782 AVoCaDO open label non-randomized study in US using ascorbic acid 50 mg IV q6h x 4 days in adults admitted to hospital with PCR confirmed COVID-19. Primary outcome is incidence of adverse events. Study estimated to be completed by August 2020.

- NCT04342728 COVIDAtoZ open label RCT in US using ascorbic acid 8000 mg/day (in 2-3 divided doses), zinc gluconate 50 mg/day, ascorbid acid with zinc gluconate or standard of care in adult outpatients who present to clinic and test positive for COVID-19. Primary outcome is time to 50% reduction in cumulative symptom score. Study estimated to be completed by April 2021.

Tocilizumab and Sarilumab

Recommendation: Recommend against the use of tocilizumab or sarilumab outside a randomized-controlled trial. If considered on an individual basis in patients with cytokine storm, it should only be done so with expert consultation (Infectious Diseases and Hematology/Rheumatology).

Tocilizumab is an interleukin-6 (IL-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 tocilizumab was used in cases of severe inflammatory response to COVID-19 with laboratory-proven high levels of IL-6 (test not readily available at most institutions). 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).

There is 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 (Gritti 2020).

There have been two other small case series reported using tocilizumab. The first was published in the Journal of Medical Virology. It is a case series of 15 patients treated with tocilizumab at a single centre in Wuhan China. Eight patients also received methylprednisolone. CRP improved in all patients but 3 patients still died, 2 had worsening disease and the rest only stabilized. It is difficult to tell how effective therapy is without a comparison group (Luo 2020). The second is a non-peer reviewed cohort study from a single hospital in France using a matched case-control design (Roumier 2020). Thirty patients with worsening respiratory parameters pre-intubation were treated with tocilizumab compared with 30 controls. Tocilizumab treated patients had a reduced need for intubation but there was no statistical difference in mortality. Overall, the numbers are small with important baseline differences between the two groups and the paper is short making the matching difficult to assess.

The World Health Organization recently held an informal consultation on IL-6 blockade. There is interest in pursuing this but unfortunately still no data. China has a trial (ChiCRT2000029765) which enrolled 63 patients. Results are still being entered into the trial database and have not yet been analyzed. No one from Italy was on the panel. The panel plans to step back and reassess whether this should be added to RCTs. One of the largest unknowns is how to select patients who may benefit from therapy. There was some discussion about the variability of IL-6 levels in infected patients.

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 2020). 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).

Sarilumab is a new humanized monoclonal antibody specific to the interleukin-6 receptor and is indicated for rheumatologic conditions. A phase 2/3 double blind, placebo controlled trial is recruiting in the U.S. for patients with severe or critical COVID-19 infection. (Clinical Trials link here).

Convalescent Plasma
Recommendation: Recommend against the use of convalescent plasma outside a randomized-controlled trial.
Convalescent plasma for treatment of COVID-19 warrants further study. We support the Canadian Blood Services in their initiatives to evaluate convalescent plasma and promote health authority partnerships in clinical trials, if locally feasible.

Convalescent plasma treatment refers to the process of drawing plasma, containing antibodies 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 an attempted treatment for a 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 radiographic 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 convalescent 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 2005: 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 the 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 workers 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 fractionated to hyperimmune IV immunoglobulin (H-IVIG) donated by 2009 H1N1 survivors vs. IVIG from patients not previously infected. While viral loads were lower in the treatment group, a subgroup analysis found a mortality benefit only for patients who received the H-IVIG with H1N1 antibodies within 5 days of symptom onset.

Summarizing the data published on convalescent plasma for the treatment of MERS, two 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). A systematic 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-haemolytic 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 a potential treatment option that warrants further investigation for the treatment of COVID-19. The Canadian Blood Services has stated that plans for clinical trials across Canada, with collaboration with the Canadian clinical research community are underway.
The U.S. Food and Drug Administration (FDA) announced on April 1, 2020 that it would allow clinical trials for using convalescent plasma to treat COVID-19 and expedited product approval. The treatment

has already begun testing in New York. Once more evidence becomes available, a careful consideration regarding the feasibility of large-scale treatment with blood products for this disease in conjunction with risks and costs will need to be undertaken.

Intravenous Immunoglobulin G (IVIG)

Recommendation: Recommend against the use of intravenous immune globulin (IVIG) outside a randomized clinical trial.

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 et 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.

Corticosteroids

Recommendation: Recommend against the routine use of corticosteroids outside a randomized-controlled trial. However, corticosteroids, via all routes of administration, may be used if *another* compelling indication is present (e.g. asthma exacerbation, refractory septic shock, obstetric use for fetal lung maturation). There is insufficient evidence at this time to recommend for or against the use of corticosteroids for acute respiratory distress syndrome (ARDS).

As of May 1st, 2020 the international community is currently divided on its recommendation for the use of corticosteroids in patients with COVID-19 and ARDS. The Surviving Sepsis Campaign Guidelines for COVID-19, a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, issued a weak recommendation to suggest the use of corticosteroids in the sickest patients with COVID-19 and ARDS. Some experts on this panel preferred not to issue a recommendation until higher quality direct evidence becomes available. The World Health Organization, Canadian Clinical Care Society, and The Australian and New Zealand Intensive Care Society (ANZICS) all recommend against the routine use of corticosteroids in COVID-19. The CTC has decided that there is insufficient evidence to make recommendations for or against the use of corticosteroids in ARDS at this time.

A new before-after study ([Fadel et al 2020](#)), labelled by the authors as "quasi-experimental" looked at 213 COVID-19 patients admitted in multiple centres across Detroit.Primary outcome was a composite of: 1)escalation of care from ward to ICU; 2) new requirement for mechanical ventilation; and 3) mortality. Pre steroids (and other system changes) 54% vs Post 35% In short, given the study design it is impossible to tell if the benefit seen is from steroids alone (0.5-1mg/kg BID x 2-3 days).

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."

Antibiotics
Recommendation: If bacterial infection is suspected, antibiotics should be initiated based on local 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/PO 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 less than 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.

Non-Steroidal Anti-Inflammatory Drugs (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.

Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (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. Conversely, it has also been hypothesized that ACE2 may have a protective effect through generation of angiotensin (1-7), which causes vasodilation. A murine model found that ACE2 down regulation by SARS-CoV worsened lung injury, which improved with treatment of an ARB (Patel 2020). 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.

Findings from observational studies to date found no association between ACE inhibitors or ARBs and risk of COVID-19 infection or clinical outcomes:

Zhang 2020-04-17: A retrospective, multicentre study from 9 hospitals in Hubei Province, China included 1128 adult patients with hypertension diagnosed with COVID-19.

- Investigated the association of mortality with ACE-I/ARB users in hypertensive patients hospitalized with COVID-19
- Mortality 3.7% (7/188) in ACE-I/ARB and 9.8% (92/940) in Non-ACE-I/ARB groups, p=0.01.
- ACE-I/ARB group had higher percentage of antiviral use (88.8% vs. 81.7%; p=0.02) and lipid-lowering therapies (22.9% vs. 10.0% p=1.51E-6).
- Propensity score-matched analysis found lower risk of all-cause mortality in ACE-I/ARB vs. non-ACE-I/ARB (HR, 0.37; 95% CI, 0.15-0.89; p=0.03), however absolute number of deaths small in ACE-I/ARB group.
- Low number of ACE-I/ARB users and deaths relative to non-ACE-I/ARB group, therefore did not have power to detect difference between ACE-I and ARB groups.

Reynolds 2020-05-01: a population-based analysis of 12,594 patients who were tested for Covid-19 in New York Langone Health network

- Assessed association between prior treatment with ACE-I, ARBs, beta-blockers, calcium-channel blockers (CCBs), or thiazide diuretics and risk of testing positive for Covid-19 and for severe illness (intensive care, mechanical ventilation or death) within all tested patients and those with hypertension
- Clinically meaningful difference defined as 10 percentage point difference in likelihood of testing positive between those on the antihypertensive and those without
- Among total patients tested, 5894 (46.8%) tested positive; a total of 4357 (34.6%) had a history of hypertension, and of those 2573 (59.1%) tested positive for Covid-19
- In the unmatched analysis, several medication classes including ACE-I and ARBs were associated with a higher likelihood of testing positive for Covid-19
- In the analysis that matched medication use and non-medication use in all Covid-19 tested patients as well as analysis that were matched in those with hypertension only, the likelihood of testing positive was greatly reduced and not clinically meaningful in those on medications for all antihypertensive classes

Mehra 2020-05-01: A retrospective cohort analysis included 8910 hospitalized patients with COVID-19 from 169 hospitals across 11 countries in Asia, Europe and North America.

- Investigated association of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with COVID-19.
- 515 of 8910 (5.8%) died in hospital; no increased risk of in-hospital death associated with ACE-I users 2.1% vs. 6.1% (OR = 0.33; 95% CI, 0.20 to 0.52) or ARB users 6.8% vs. 5.7% (OR = 1.23; 95% CI 0.87 to 1.74).
- Multivariable logistic-regression model found age > 65 y.o., CAD, CHF, cardiac arrhythmia, COPD and smoking status were associated with higher risk of in-hospital death.
- Tipping-point analysis to assess potential effect of unmeasured confounders found an unobserved binary confounder with prevalence of 10% in study population would need OR ≥ 10 for either ACE-I or statins to have 95% CI crossing OR of 1

Mancia 2020-05-01: A population-based case-control study in Lombardy region of Italy of 6272 COVID-19 cases matched with 30 759 controls.

- Investigated the association between ACE-I and ARB users with risk of COVID-19 diagnosis in beneficiaries of the Regional Health Service (≥ 40 y.o.)
- For each case patient, ≤ 5 controls were randomly selected from target population matched for sex, age at index date and municipality of residence.
- Larger percentage of case patients used ACE-I (23.9% vs. 21.4%) and ARBs (22.2% vs. 19.2%) compared to controls. CCBs, B-blockers and diuretics were also used more frequently.
- After multivariable adjustment, neither ACE-I or ARBs had a significant association with risk of COVID-19.
- Mild-moderate and severe infection (need for ventilation or death) were not associated with ACE-I or ARB use

There are currently 4 clinical trials ongoing examining losartan in adult patients with COVID-19 in both outpatient and hospital settings on mortality, ICU admission, hospitalization and length of hospitalization (NCT04340557, NCT04311177, NCT04335123, NCT04312009)

Venous Thromboembolism (VTE) prophylaxis

Recommendation: Suggest enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in critically ill patients with COVID-19. Consider enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in hospitalized ward-based patients with COVID-19. This dose was selected to reduce incident VTE and potentially save health care resources with patient transport and minimize risk of COVID-19 transmission to staff and others. Suggest even higher doses of enoxaparin for hospitalized patients with weight above 100 kg or BMI above 40 kg/m^2.

Rates of VTE in general hospitalized patients with COVID-19 are expected to be similar to patients with inflammatory disorders or sepsis. Severe COVID-19 infections appear to present with a hypercoagulable state although the incidence of acute VTE remains uncertain and varies between publications. Based on observational data, severe thrombocytopenia is uncommon from COVID-19 while D-dimer levels are typically elevated (above 500 mcg/L) in 50% of COVID-19 patients (Guan 2020-02-28), reflecting inflammation and/or infection. Coagulopathy from disseminated intravascular coagulation is seen in severe advanced disease, with associated high mortality. One study of 191 patients from Wuhan, China reported a strong association between elevated D-dimer levels above 1000 mcg/L and mortality (Zhou 2020-03-28). This finding is limited by the study's small sample size, lack of adjustments for multiple comorbidities, and wide confidence interval.

A small study of 81 patients from China noted that 25% of patients developed lower extremity VTE; however, use of pharmacologic prophylaxis was not reported (Cui 2020-04-09). In this study, risk factors for incident VTE included older age, elevated PTT, and elevated D-dimer. A cohort of 184 ICU patients with COVID-19 from the Netherlands showed incidence of thrombotic events (VTE, ischemic stroke, myocardial infarction, or systemic embolism) occurred in 31% [95% CI 20 to 41%] and VTE in 27% [95% CI 17 to 37%] despite receiving standard VTE prophylaxis (Klok 2020-04-10). Predictors of thrombosis included older age, elevated PT, and elevated PTT.

Elevated D-dimer levels may reflect both a hypercoagulable state and underlying inflammation due to its nature as a non-specific acute phase reactant. Preliminary observational data suggest increased incidence of VTE events in critically ill patients; however, the available data is scant and VTE incidence may vary depending on institutional practice. There is no robust clinical evidence to support therapeutic full anticoagulation for treatment of COVID-19 in the absence of other compelling indications.

Although initial publication focused on VTE rates in critically-ill patients with COVID-19, recent studies have suggested that the risk of thromboembolism in patients admitted to the ICU far exceeds those admitted to the general ward. Generally, rates of VTE in ward patients appear to be similar to those without COVID-19, and intensified or therapeutic anticoagulation, at least thus far, has not been shown to be of further benefit in non-critically ill patients. As such, new evidence is pointing towards a varied approach dependant on illness severity.

The following sections summarize the currently available evidence for VTE rates and prophylaxis, stratified by disease severity in patients with COVID-19.

VTE in critically ill patients admitted to ICU

Tang 2020-03-27: Large retrospective study of 449 critically ill patients admitted to a single ICU in a Chinese hospital with COVID-19.

- The purpose of the study was to compare mortality for those that received VTE prophylaxis to those that did not.
- Only 99 (22%) patients received VTE prophylaxis for 7 days or more mainly with enoxaparin 40 to 60mg SQ daily.
- There was no difference in the primary outcome of 28-day mortality in the multivariate analysis between users of heparin and non-users (30.3% vs. 29.7%).
- In patients with the most elevated D-dimers (greater than 3 ug/ml, or 6 times ULN), there was a difference in mortality between those that received VTE prophylaxis to those that did not (32.8% vs. 52.4%), but the raw number of patients in this category is not reported. It is not reported whether mortality was due to thrombosis.

Yin 2020-04-03: A subsequent analysis of the same 449 patients from Tang 2020-03-27, this time compared to 104 patients admitted with non-COVID pneumonia to the ICU.

- The mortality in the COVID-19 patients was 29.8%, compared to 15.4% in the non-COVID patients (p<0.01).
- The same proportion of patients received VTE prophylaxis in the two groups (22% vs. 21.2%), for 7 days or longer.
- As reported by Tang 2020-03-27, no difference in mortality was observed between those that received VTE prophylaxis to those that did not in both groups (30.3% vs. 29.7%; 13.6% vs. 15.9%).
- Interestingly, the average D-dimer of non-COVID patients was higher than in COVID-19 patients, but the difference was not statistically significant (2.52 mg/L vs 1.94 mg/L). Other coagulation measures such as PT and platelet counts were no different.

Cui 2020-04-09: A retrospective study from Wuhan, China of the 81 patients admitted to a single ICU with severe COVID-19.

- Definition and detection methods of VTEs were poorly reported; 20/81 patients (25%) developed lower extremity VTEs.
- The study compared the 20 patients with VTE to the remaining 61 patients who did not develop VTE using simple statistics that did not adjust for covariates.
- Risk factors for VTE incidence was older age, elevated PTT and elevated D-dimer.
- 8 of 20 patients who developed VTE died, but no mortality outcome was reported for the total study population or those who did not develop thrombosis.
- The authors specifically stated that none of the patients received pharmacologic VTE prophylaxis, but discussed that patients with D-dimers over 3 mg/L received therapeutic anticoagulation for treatment of presumptive thrombus.

Klok 2020-04-10: Prospective cohort study in 3 Dutch hospitals of 184 patients admitted to the ICU for severe COVID-19.

- Composite outcome symptomatic PE, DVT, ischemic stroke, myocardial infarction, systemic arterial thrombosis: 31% (95%CI 20-41%)
- VTE confirmed by ultrasound or CT PE: 27% (95% CI 17-37%)
- All patients received LMWH prophylaxis with nadroparin at doses of 2,850 units SQ daily up to 5,700 units SQ BID based on weight. **Note: Nadroparin 4000 units is equivalent to enoxaparin 40mg.**
- Age, prolonged PT and PTT were independent predictors of thrombotic complications.
- The study concluded that the observed prevalence of VTE was alarmingly high and likely underestimated as events majority of patients still remained in ICU at time of writing
- No other outcomes (for example mortality) were reported.

Helms 2020-04-22: A multicentre prospective cohort study in four ICUs in French tertiary care hospitals of 150 patients with COVID-19:

- 64/150 (42%) of patients had clinically relevant thrombotic complications (15% had segmental or larger PEs; the rest of the thrombotic complications included were subsegmental PEs, cerebral ischemic events, and extracorporeal circuit thrombosis).
- All patients received LMWH at 4,000 units per day (equivalent to enoxaparin 40mg/day) or if contraindicated, unfractionated heparin at 5-8 units/kg/hr (equivalent to 8,000 units to 13,500 units per day for a 70 kg patient).
- 28 of 29 patients (96.6%) receiving continuous renal replacement therapy experienced circuit clotting despite prophylaxis.
- As a secondary analysis, the study compared COVID-19 patients with ARDS (N=77) to those with ARDS due to other causes (N=145). Observed VTE was higher in those with COVID-19 (11.7% vs. 2.1%; p < 0.05).

Llitjos 2020-04-22: A retrospective study in 2 French ICUs of 26 patients screened for VTE with complete duplex ultrasound (CDU) between day 1 and day 3 of their ICU stay.

- 31% (N=8) were treated with prophylactic anticoagulation and 69% (N=18) were treated with therapeutic anticoagulation.

- The cumulative rate of VTE in patients was 69% (N=18). The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared to the full anticoagulation group (100% vs 56% p=0.03).
- The generalizability and clinical relevance of the study is significantly reduced by inclusion of potentially asymptomatic VTE through wide-spread screening, particularly as most patients did not experience PE.

With the exception of the Yin 2020-04-03 and Helms 2020-04-22, the results of the above-mentioned studies do not directly compare the rates of VTE in the ICU with COVID-19 to those in the ICU for other reasons. As such, it is difficult to infer whether the observed high risk of VTE is due to COVID-19 alone, or variables such as differing standards of care, higher acuity of patients admitted to ICUs outside of Canada or lack of system capacity in a pandemic setting. To put these rates in a Canadian context, a landmark trial of VTE prophylaxis in 3764 critically ill patients (PROTECT 2011) is often cited as an indirect comparison. In this multicentre randomized trial, ICU patients received either dalteparin (5000 units SQ daily plus placebo once daily) or unfractionated heparin (5000 units SQ BID). At baseline, the average APACHE II score was 21, 90% were mechanically ventilated, 45% were on vasopressors, and 32% were on ASA. In both treatment arms, the rate of proximal leg VTE was 5-6% and PE was 1-2%. The rate of any VTE was 8-10%. These rates give insight into the expected baseline prevalence of VTE in ICU patients on prophylaxis locally, and appear lower compared to the rates currently published for critically ill COVID-19 patients.

VTE in non-critically ill patients admitted to the general ward

Published data characterizing the prevalence of VTE in patients outside of the ICU are sparse, and non-critically ill patients have not been the focus of many publications pertaining to COVID-19 and anticoagulation. Two studies make explicit comparisons between severely and non-severely ill patients, and are reviewed below. No society guideline or statement has made any discerning comments regarding patients based on severity of illness or location (ICU vs. ward). The following data can be applied to non-critically ill patients:

Middledorp 2020-04-19: A single-center cohort study from the Netherlands of 198 hospitalized patients with COVID-19:

- 63% (N=124) were admitted to the ward and 39% (N=74) were treated in the ICU at some point during their hospital stay.
- All patients received intensified VTE prophylaxis with weight-based nadroparin (2,850 or 5,700 IU BID), which is equivalent to 30-60mg of enoxaparin BID.
- The primary outcome was objectively diagnosed, but not necessarily symptomatic VTE, which included PE, DVT and catheter-related thrombosis.
- ICU patients were more likely to be male and had higher D-dimers (2.1 mg/L vs. 1.1 mg/L).
- ICU patients were much more likely to be screened for asymptomatic VTE with doppler US than ward patients (34/74 of ICU patients vs. 18/124 ward patients).
- There were 33 (17%) VTEs identified; 22 (11%) were symptomatic and 11 (5.6%) were incidental.
- Of the 33 VTEs, 29 occurred in ICU patients and 4 in ward patients; ICU stay was independently associated with VTE risk, with a HR of 6.9 (95%CI 2.8-17).
- The study characterized the high prevalence of VTE in critically-ill patients despite intensified anticoagulation, and the much lower risk of VTE in ward-based patients.

Lodigiani 2020-04-23: A retrospective study of 388 patients hospitalized in a teaching hospital in Milan, Italy.

- 84% (N=326) of patients were admitted to the ward and 16% (N=62) to the ICU
- Thromboembolic events occurred in 9 patients in the ICU, but only in 21 of ward patients. Precise rates for using the 388 study patients could not be calculated as cases that were still in hospital were not considered "closed" and not included in the primary outcome. The cumulative rate was reported as 27.6% in the ICU population and 6.6% in the ward population.
- Approximately half of the events were arterial thromboembolism (stroke and ACS), and half were VTE
- All patients in the ICU were anticoagulated, while 75% of ward patients received thromboprophylaxis; regimens varied from full, intermediate and standard doses
- Of the 21 ward patients, 12 experienced VTE, 6 experienced stroke and 3 suffered an ACS
- Of the 21 ward patients with events, 6 received full anticoagulation, 7 were on intermediate doses, 4 were on standard doses and 2 were not anticoagulated
- There was no association with the dose of thromboprophylaxis received and the rate of venous or arterial thromboembolism
- The study confirms previous findings that the rate of thromboembolic events in the ICU is much higher than on the general wards, and the rates of VTE in these populations appear consistent with previously reported VTE rates. Enhanced anticoagulation regimens in ward patients do not seem to confer additional protection.

A similar study currently in press (citation pending) from the US produced similar results. Of 215 patients hospitalized with COVID-19, 16 had VTE events, and 15 out of 16 were critically ill patients in the ICU. 80.8% of patients received standard dose enoxaparin; the remainder of patients received therapeutic anticoagulation. All observed events occured in patients receiving standard prophylactic doses of enoxaparin, suggestive that once daily dosing may not be sufficient for patients in the ICU, but that the incidence of VTE in ward patients is low and intensified enoxaparin dosing in this population is unlikely to make a clinically significant difference.

Based on the lack of representation of non-severely ill patients treated outside of the ICU, no conclusions about the risk of VTE and optimal anticoagulation regimens for such patients can be made. However, preliminary studies show that regardless of the regimen used, VTE rates in ward patients are much lower than in critically ill patients, and increasing the anticoagulation dose may not be warranted.

Laboratory abnormalities in patients with COVID-19
Tang 2020-02-19: A retrospective study of characteristics of 183 consecutive patients with COVID-19 admitted to a hospital in Wuhan, China.

- While the proportion of ward vs. ICU patients was not stated, the study included "all-comers", implying that non-ICU patients were captured.
- Anticoagulation parameter abnormalities were associated with mortality; however the results were not stratified by disease severity.

Zhou 2020-03-09: A retrospective study of all comers with COVID-19 admitted to 2 hospitals in Wuhan, China.

- 38% of patients (N=72) had "general" disease severity; 35% (N=66) were severely ill and 28% (N=53) were in critical condition. The qualifiers for these categories were not mentioned.
- None of the 72 patients with "general" disease died, while the mortality of the critically and severely ill patients was 66/119 (55%).
- While characteristics of survivors vs. non-survivors were reported; statistically significantly different variables between groups relevant to coagulation included a 0.8s shorter PT and a higher D dimer (5.2 ug/ml vs. 0.6 ug/ml). Since no patient with "general" disease severity died, it can be inferred that coagulation parameters are less likely to be abnormal in the non-severely or critically ill population, which are likely admitted to the ward.

Lippi 2020-03-13: A meta-analysis of baseline characteristic of COVID-19 patients from 9 studies from China and Singapore.

- 1779 patients were included and 77.6% (N=1380) had non-severe COVID-19, which was mainly defined as admission to an non-ICU ward, not receiving mechanical ventilation or absence of ARDS
- While the results were not consistent between studies, those with severe COVID-19 had lower platelet counts by 31 x 10(9) cells/L.
- A sub-analysis of 3 studies that included survival as an outcome showed that mortality was associated with a platelet drop; however it is not clear what proportion of ward-based patients was represented in this analysis.

Zhang 2020-04-19: A retrospective study of 343 patients to evaluate whether elevated D-dimer levels predict mortality in patients with COVID-19 in Wuhan, China.

- D-dimers were collected within 24 hours after admission.
- The average patient was 65 years old, 50% were female and 35% with underlying comorbidities (hypertension, diabetes, CAD).
- Patients with D-dimer levels >2ug/ml was a significant predictor of death (HR 51.5, 95% CI 12.9-206.7) with a sensitivity of 92.3% and a specificity of 83.3%.

Elevated D-dimer levels may reflect acute VTE however, this test is non-specific and can be elevated in a variety of other conditions (eg: malignancy, inflammatory conditions and infections). Preliminary observational data suggests there may be a correlation with elevated D-dimer levels and increased incidence of VTE in critically ill patients. Other data suggests high D-dimer levels (3-4 fold or >1000-2000 mcg/L) are associated with high mortality. Currently, there is no evidence to support therapeutic anticoagulation based on D-dimer levels in COVID-19 patients in the absence of other compelling indications.

Recently, a Canadian trial led by St. Michael's Hospital has been designed to evaluate the optimal prophylactic regimen in non-ICU patients. The RAPID COVID COAG study is a pragmatic, randomized, controlled trial of therapeutic coagulation vs. standard of care of non-critically ill hospitalized patients with D-dimer elevated above 2 mg/L. The primary objective of the study is to evaluate whether full-dose, therapeutic anticoagulation in those with laboratory risk factors can prevent the development of critical illness, VTE and reduce mortality.All hospitalized patients with COVID-19 should receive pharmacologic VTE prophylaxis, unless contraindicated. This is consistent with statements from the American Society of Hematology as of April 17, 2020. Currently, the standard VTE prophylaxis regimen in BC 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 commonly used. The potential benefits with a higher daily dose of prophylactic anticoagulation include greater protection from 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; accordingly, 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 use of lopinavir/ritonavir[#] outside a randomized-controlled trial.

2. Remdesivir
   Recommendation: Recommend against the use of remdesivir[#] outside a randomized-controlled trial.

3. Chloroquine and Hydroxychloroquine
   Recommendation: Recommend against the use of chloroquine and hydroxychloroquine[#] for treatment or prophylaxis outside a randomized-controlled trial.

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

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

6. Colchicine
   Recommendation: Recommend against the use of colchicine[#] for treatment or prophylaxis outside a randomized-controlled trial.

7. Ascorbic Acid
   Recommendation: Recommend against the use of ascorbic acid for treatment or prophylaxis outside a randomized-controlled trial.

8. Tocilizumab and Sarilumab
   Recommendation: Recommend against the use of tocilizumab or sarilumab[#] outside a randomized-controlled trial. If considered on an individual basis in patients with cytokine storm,

it should only be done so with expert consultation (Infectious Diseases and Hematology/Rheumatology).

9. Convalescent Plasma
   Recommendation: Recommend against the use of convalescent plasma[#] outside a randomized-controlled trial.

10. Intravenous Immunoglobulin G (IVIG)
    Recommendation: Recommend against the use of IVIG outside a randomized-controlled trial.

11. Corticosteroids
    Recommendation: Recommend against the routine use of corticosteroids outside a randomized-controlled trial. However, corticosteroids, via all routes of administration, may be used if *another* compelling indication is present (e.g. asthma exacerbation, refractory septic shock, obstetric use for fetal lung maturation). There is insufficient evidence at this time to recommend for or against the use of corticosteroids for acute respiratory distress syndrome (ARDS).

12. Antibiotics
    Recommendations: If bacterial infection is suspected, antibiotics should be initiated based on local institutional antibiograms and sensitivities.

13. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
    Recommendation: Recommend acetaminophen use preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.

14. Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (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.

15. Venous Thromboembolism (VTE) prophylaxis
    Recommendation: Suggest enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in critically ill patients with COVID-19. Consider enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in hospitalized ward-based patients with COVID-19. This dose was selected to reduce incident VTE and potentially save health care resources with patient transport and minimize risk of COVID-19 transmission to staff and others. Suggest even higher doses of enoxaparin for hospitalized patients with weight above 100 kg or BMI above 40 kg/m^2.

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

[#] Denotes that a clinical trial of named therapy is currently planned or underway in British Columbia. Links below for registered trials in Canada and British Columbia.

Canada:
https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-clinical-trials/list-authorized-trials.html

British Columbia:
https://bcahsn.ca/covid-19-response/inventory/

*Recommendations are consistent with guidelines from the World Health Organization (WHO), the Surviving Sepsis Campaign (SSC) (a joint initiative of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)), the Public Health Agency of Canada (PHAC), the Canadian Critical Care Society (CCCS), the Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and The Australian and New Zealand Intensive Care Society (ANZICS)

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SEARCH STRATEGY:

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

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