



Coronavirus COVID-19

BC Centre for Disease Control | BC Ministry of Health



Unproven Therapies for COVID-19

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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 a 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 April 10, 2020, the Cochrane COVID-19 Study Register lists 490 interventional studies of which 285 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

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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. tocilizumab or sarilumab[#]
8. convalescent plasma[#]
9. intravenous immunoglobulin (IVIG)
10. corticosteroids
11. 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**)/Ibuprofen, Angiotensin Converting Enzyme (**ACE**) inhibitors and Angiotensin Receptor Blockers (**ARBs**), Venous Thromboembolism (**VTE**) prophylaxis, and blood products 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, ascorbic acid, 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 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 Canadian Critical Care Society ([CCCS](#)), the Association of Medical Microbiology and Infectious Disease Canada ([AMMI](#)), The Australian and New Zealand Intensive Care Society ([ANZICS](#)), and the Centers for Disease Control ([CDC](#)) have made recommendations for treatment of COVID-19 but they are limited to supportive care. All support the enrollment of patients in clinical trials for currently unproven therapies. The WHO updated their [guideline document](#) regarding clinical management of

severe COVID-19 on March 13, 2020, with a main recommendation of ***“Investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials.”***

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.**

https://www.who.int/docs/default-source/coronaviruse/who-ncov-crf.pdf?sfvrsn=84766e69_4

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. Oral ribavirin is available in Canada, and is currently non-formulary. Inhaled ribavirin is restricted to the treatment of RSV, but has not been evaluated for the treatment of coronaviruses.

Human Data

[Cao 2020](#): Randomized Controlled Trial of 199 patients with COVID-19 treated in Wubei, China at the peak of the outbreak

- 100 patients were randomized to receive lopinavir/ritonavir for 14 days and 99 to receive standard of care
- Patients included were those who had difficulty maintaining O2 saturations of >94% on room air; many patients were severely ill and received treatment late as evidenced by the nearly 25% mortality.
- The primary outcome was clinical improvement by 2 points measured by a 7-point ordinal scale, or discharge from hospital, whichever came first.
- The trial did not find a difference between the two groups in the primary outcome. Viral shedding was no different between groups. Mortality was lower in the treatment arm but was not statistically significant.
- 13.8% of patients in the treatment arm had to stop the drug because of adverse-effects such as gastrointestinal intolerance and laboratory abnormalities; but serious adverse events were more common in the control arm.
- An interim analysis showed that the trial was underpowered, however, enrollment was suspended as remdesivir became available.

[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](#)).

Unfortunately, remdesivir is not commercially available and not approved by the FDA. Remdesivir was used on the basis of Compassionate Use for one of the first patients with COVID-19 in the United States ([Holshue 2020](#)). The patient improved rapidly with 7 days of treatment and no adverse effects. Viral PCR was negative for the virus after one day of therapy. Since then, a case series of patients receiving remdesivir as part of the compassionate use program has also been published.

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

- Patients were eligible to receive a 7-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.

Remdesivir is being used in several phase 3 trials in the United States sponsored by National Institute of Allergy and Infectious Diseases (NIAID). Enrollment in these trials is not feasible in Canada at this time. There are four other trials registered world-wide.

The process of obtaining remdesivir in Canada for Compassionate Use (CU) outside of the abovementioned RCTs has been verified with the company (Gilead) and Health Canada. It consists of a multi-step process that includes an application on the Gilead website, as well as a Special Access Program (SAP) application to Health Canada. The inclusion criteria for the use of remdesivir appear prohibitive; hospitalized patients who have a positive test for SARS-CoV2 on ventilatory support but not receiving vasopressor support or experiencing organ failure. In addition, due to increased demand the criteria for eligibility has changed rapidly and become more restrictive. Gilead has suspended all compassionate access except for pregnant women and patients under 18 years of age and they are developing an expanded access program that will be required to gain access to medication with details to follow. Currently no applications for compassionate access are being processed outside above cases.

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 April 16, 2020, the Cochrane COVID-19 Study Register lists 70 randomized interventional studies with reference to hydroxychloroquine as one of the study groups.

Human Data

As of April 16, 2020, there are at least 10 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; one is a propensity-matched case control study; one is a case control series; and three are case series with no control arm. Of the five randomized studies, three are published in non-peer reviewed manuscript databases, one is published as an uncorrected manuscript, 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.

[Tang 2020-04-14](#): randomized, open-label multi-center study at 16 hospital sites with 150 patients in China (non-peer reviewed publication but registered trial ChiCTR2000029868)

- compared hydroxychloroquine 400 mg three times daily x 3 days, then 400 mg twice daily to complete 2 weeks (n=75) vs usual care (n=75)
- trial originally planned to enrol 360 patients but the study was terminated early due to an interim analysis at 150 patients where the investigators found “promising results into clinical benefits that could save lives”. This statement was based off a very small post-hoc subgroup analysis in patients who did not receive “antivirals” where hydroxychloroquine subgroup showed better symptom alleviation than control group: 8/14 vs 1/14; they also noted CRP was reduced more in the overall hydroxychloroquine group but the baseline CRP was higher in the hydroxychloroquine group and the actual differences in change from baseline were of questionable statistical and clinical significance: 6.99 vs 2.72 mg/L, p=0.045 (not adjusted for multiple comparisons)
- when looking at the entire study sample, there were no differences in its primary outcome of negative viral studies at any time point; there were also no differences in clinical symptoms at any time point
- more adverse effects were noted in the hydroxychloroquine group 30% vs 8.8%, p=0.001 and 2 patients in the hydroxychloroquine group developed serious adverse events
- limitations of this study are numerous; the main limitations are its open-label nature (performance and detection bias) and the study’s premature termination based on questionable interpretation of a small post-hoc subgroup analysis that showed weak and imprecise benefit for hydroxychloroquine; in addition, patients were enrolled into this study after a mean of 17 days which leads us to question its generalizability; overall, this study does not offer credible evidence to support hydroxychloroquine use in treatment of hospitalized patients with COVID-19

[Mahevas 2020-04-14](#)

- propensity score matched cohort analysis at four hospitals with 181 patients in France (non-peer reviewed publication)
- included hospitalized patients on general medical wards requiring oxygen by nasal prongs or face mask
- compared hydroxychloroquine 600 mg daily (n=84) vs usual care (n=97) and matched patients using 15/19 variables such as age, gender, comorbidities, immunosuppressants, and physiologic variables
- no differences found in primary outcome of transfer to ICU or death at 7 days, 16/84 (20.5%) vs 21/97 (22.1%) RR 0.91 (0.48 to 1.81)
- also no differences in death at 7 days or incidence of ARDS
- ECG changes in hydroxychloroquine group 8/84 (9.5%) that required treatment discontinuation after 4 days
- this study was a well-performed observational study with adequate matching of patients and measures were taken to minimize the effects of time-dependent bias; no significant differences were in efficacy outcomes were demonstrated in this study

[Borba 2020-04-11](#): CLORO-COVID study; preliminary safety results of a single-center randomized, double-blinded clinical trial currently with 81 hospitalized patients enrolled in Brazil (non-peer reviewed publication but registered trial NCT04323527)

- 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](#): 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 uncorrected manuscript and 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](#): 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 sample size and its lack of control group
- It is 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.
- 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](#): 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 the time of their writing, 1/80 patients died, 14/80 patients still hospitalized (3/80 patients admitted to ICU), and 65/80 patients discharged home.
- this study has numerous limitations including its lack of control group, its study population's overall lack of need for oxygen support which argues against need for hospitalization and antiviral treatment in the first place, and unclear clinical relevance of repeated viral PCR studies and cultures.

[Chen 2020-03-24](#): 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 after randomization and no difference was observed between groups (hydroxychloroquine 13/15 (86.7%) vs usual care 14/15 (93%); NS)
- No difference was observed in secondary outcomes such as time to normothermia or radiographic progression on CT
- All patients showed improvement at follow-up exam
- Overall, this trial was a negative finding study with small numbers and with possible confounders due to co-treatments with interferon and umifenovir

[Gautret 2020-03-20](#): Case-control series of 42 hospitalized patients in France with positive viral study (peer-reviewed publication however one of the authors of this study is the Editor-in-Chief of the publication journal - International Journal of Antimicrobial Agents; 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.
- The primary endpoint was virological clearance on day 6.
- 6 patients in the study were asymptomatic throughout the study.
- The study reported that COVID-19 PCR was negative in 100% of patients on day 6 who took both drugs, 57.1% in those who received hydroxychloroquine alone, and 12.5% of those who did not receive treatment.

- However, 6 patients treated with hydroxychloroquine were excluded from the analysis as viral samples were unavailable due to transfer to ICU, discharge home, treatment cessation, or death.
- No clinical endpoints were reported and the endpoint for negativity was a CT value ≥ 35 which differs from typical virological studies.
- The main limitations of this study include its non-randomized nature and lack of blinding which introduces selection, performance and detection bias, its small sample size, its significant loss to follow-up (attrition bias), and lack of clinical outcomes. In addition, a significant proportion of patients were asymptomatic which argues against generalizability of study results.
- Due to limitations stated above, meaningful clinical conclusions from this study cannot be derived.

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 μ M, implying that therapeutic levels could be achieved in humans with a 500 mg dose ([Wang 2020](#)). The EC₅₀ of chloroquine for SARS is 4.4 to 8.8 μ M ([Colson 2020](#)), suggesting that chloroquine could be more effective against COVID-19 than SARS.

Hydroxychloroquine might be more potent for COVID-19 than chloroquine. Hydroxychloroquine’s EC₅₀ is 0.72 μ M 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 Zhejiang, China. All 36 children received *interferon alfa* by aerosolization 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.

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](#)).

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:

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 \geq 60 kg [0.5 mg PO daily if <60 kg] vs. usual medical treatment. The endpoints are time for CRP levels to be $>3\times$ UNL, 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.

In vitro Data:

SARS-CoV-2 proteins such as viroporins E, 3a and 8A involved in viral replication appear to activate NLRP3 ([Castaño-Rodríguez 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](#)).

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 (<https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1.full.pdf>). The World Health Organization recently held an informal consultation on IL-6 blockade (https://www.who.int/blueprint/priority-diseases/key-action/Expert_group_IL6_IL1_call_25_mar2020.pdf?ua=1). 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 April 3, 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.

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 β 1b (rIFN β 1ba) did not reduce mortality in ARDS patients, but in the subgroup of patients receiving corticosteroids, rIFN β 1ba 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 ([Rygaard 2018](#), [Rochweg 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. 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.

A clinical trial ongoing examining losartan in adult patients with COVID-19 requiring hospitalization with primary outcome of sequential organ failure assessment (SOFA) respiratory score is currently underway (NCT04312009).

Venous Thromboembolism (VTE) prophylaxis

Recommendation: Suggest enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in hospitalized patients with COVID-19. This dose was selected to reduce 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/m².

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. 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.

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](#)).

Publications highlighting coagulation markers in COVID-19

- [Tang 2020-02-19](#): Elevated D-dimer (2.12 vs 0.61 ug/mL, $p < 0.001$) in non-survivors vs. survivors [n=183 consecutive patients with confirmed COVID-19 pneumonia]
- [Guan 2020-02-28](#): Higher D-dimer levels in severely ill COVID-19 patients [n=1099 confirmed COVID-19 patients]
- [Lippi 2020-03-13](#): Meta-analysis (9 studies: 1799 patients, 399 with severe COVID-19) severe COVID-19 infections typically have more pronounced thrombocytopenia. Platelet count could be a useful parameter to determine mild vs. severe COVID-19 disease.
- [Zhou 2020-03-28](#): Elevated D-dimer (>1 ug/mL) in 81% of non-survivors vs. 24% of survivors, elevated PTT in non-survivors compared to survivors ($p < 0.0001$) [n=191 confirmed COVID-19 patients]
- [Cui 2020-04-09](#): Observed higher incidence of VTE, higher D-dimer and PTT levels in COVID-19 patients in the ICU, but use of pharmacological prophylaxis was not reported.

Publications highlighting use of anticoagulants in COVID-19

- [Tang 2020-03-27](#): Observational retrospective study showed patients treated with heparin had lower 28-day mortality ($p = 0.029$). Unclear which dose was used.
- [Thachil 2020-04-02](#): Commentary: Heparin has anticoagulation, anti-inflammatory, endothelial protection and antiviral properties that could be beneficial in COVID-19.
- [Yin 2020-04-03](#): Patients with high sepsis-induced coagulopathy (SIC) score or elevated D-dimer levels may benefit from anticoagulant therapy (mainly LMWH) [n=449 patients with severe COVID-19 infections].
- [Wang 2020-04-08](#): case report: tPA therapy may improve outcomes in COVID-19 patients with ARDS, with transient improvement in oxygenation.
- [Klok 2020-04-10](#): all patients received at least standard doses of LMWH prophylaxis with nadroparin; VTE rates were 27% (95% CI 17 to 37%) of which PE was the most common thrombotic event [n=184 patients admitted to ICU in Netherlands with COVID-19 pneumonia]

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. 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).
8. Convalescent Plasma
Recommendation: Recommend against the use of convalescent plasma[#] outside a randomized-controlled trial.
9. Intravenous Immunoglobulin G (IVIG)
Recommendation: Recommend against the use of IVIG outside a randomized-controlled trial.
10. 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).
11. Antibiotics
Recommendations: If bacterial infection is suspected, antibiotics should be initiated based on local institutional antibiograms and sensitivities.
12. 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.
13. 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.
14. Venous Thromboembolism (VTE) prophylaxis

Recommendation: Suggest enoxaparin 30 mg SC bid as the preferred dose for VTE prophylaxis in hospitalized patients with COVID-19. This dose was selected to reduce 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/m².

15. Other investigational therapies

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

***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)**

Contributors

Dr David Sweet MD (Chair)	Critical Care Physician, Vancouver General Hospital & Clinical Lead for Sepsis, BCPSQC
Dr John Boyd MD	Critical Care Physician, St Paul's Hospital
Dr Luke Chen MD	Hematology Physician, Vancouver General Hospital
Dr Dana Cole PharmD	Regional Director, Pharmacy Services, Northern Health
Dr Greg Deans MD	Infectious Diseases Physician, Fraser Health (Surrey)
Dr Josh Douglas MD	Infectious Diseases and Critical Care Physician, Lions Gate Hospital
Dr Ryan Foster MD	Critical Care Physician, Kelowna General Hospital
Dr Sean Gorman PharmD	Critical Care Pharmacist and Pharmacy Coordinator, Interior Health Authority
Dr Jennifer Grant MD	Infectious Diseases and Medical Microbiology Physician, Vancouver General Hospital
Dr Andrew Guy MD	Resident Physician, Emergency Medicine
Dr Abu Hamour MD	Infectious Diseases Physician, University Hospital of Northern British Columbia Hospital
Dr Shahin Jamal MD	Rheumatology Physician, Vancouver General Hospital

Dr I fan Kuo PharmD	Director Optimal Use and Evaluation Branch, Pharmaceutical Services Division, Ministry of Health
Dr Tim Lau PharmD	Infectious Diseases Pharmacist and Clinical Supervisor, Vancouver General Hospital
Dr Allison Mah MD	Infectious Diseases (Transplant) Physician, Vancouver General Hospital
Dr Gregory Mah PharmD	Critical Care Pharmacist, Vancouver General Hospital
Dr Rita McCracken MD PhD	Family Physician, Long Term Care, Vancouver Coastal Health
Dr John Mcewen MD	Anesthesia Physician, Vancouver General Hospital
Dr Graydon Meneilly MD	Internal Medicine Physician and Department Head, Internal Medicine, Vancouver General Hospital
Dr Anish Mitra MD MPH	Critical Care Physician, Surrey Memorial Hospital
Dr Val Montessori MD	Infectious Diseases Physician, St. Paul's Hospital
Dr Srinivas Murthy MD	Infectious Diseases and Critical Care Physician, Children's Hospital & PI for CATCO trial
Dr Cesilia Nishi PharmD	Infectious Diseases Pharmacist, Vancouver General Hospital
Dr Daniel Ovakim MD	Critical Care Physician, Royal Jubilee Hospital
Dr Elizabeth Parfitt MD	Infectious Diseases Physician, Royal Inland Hospital
Dr Eric Partlow MD	Infectious Diseases Physician, Royal Jubilee Hospital
Dr Nilu Partovi PharmD	Transplant Pharmacist and Clinical Coordinator, Vancouver General Hospital
Dr Jolanta Piszczek PharmD MSc	Infectious Diseases Pharmacist, Royal Jubilee Hospital
Dr Natasha Press MD	Infectious Diseases Physician, St. Paul's Hospital
Alicia Rahier BSc Pharm, ACPR	Infectious Diseases Pharmacist, University Hospital of Northern British Columbia Hospital
Dr Marietjie Slabbert MD	Critical Care Medicine Physician, University Hospital of Northern British Columbia Hospital
Dr Ted Steiner MD	Infectious Diseases Physician and Division Head of Infectious Diseases, Vancouver General Hospital
Dr Rob Stenstrom MD PhD	Emergency Medicine Physician and Research Director, St Paul's Hospital
Dr Adam Thomas MD	Critical Care Fellow, Emergency Medicine Physician
Dr Krisztine Vasarhelyi PhD	University of British Columbia
Dr Jerry Vortel MD	Infectious Diseases Physician, Richmond General Hospital
Dr Alissa Wright MD MSc	Infectious Diseases (Transplant) Physician, Vancouver General Hospital

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
Search Date: March 19, 2020

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