Clinical Reference Group SBAR: Therapies for COVID-19

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The British Columbia COVID-19 Therapeutics Committee (CTC) meets bi-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 242 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 221 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.

Remdesivir is currently the only antiviral agent conditionally approved in Canada for treatment of COVID-19. Certain immunomodulatory treatments have been studied and shown positive results, for example corticosteroids and IL-6 inhibitors such as tocilizumab, while others continue to be investigated in clinical trials. Concomitantly, several well-designed studies have shown various therapies to have no effect or pose safety concerns. Agents of particular interest currently include monoclonal antibodies against the spike protein, as well as oral direct acting antivirals currently in the development pipeline. The most significant advancement in COVID-19 therapeutics is dexamethasone and tocilizumab, with survival benefit, followed by data surrounding anticoagulation for hospitalized patients. While less

impactful, colchicine, inhaled budesonide and remdesivir have been shown to decrease time to recovery or improve symptoms in a variety of patient populations. As of January 16, 2021, the Cochrane COVID-19 Study Register lists over 4300 interventional trials. 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. corticosteroids
2. IL-6 blockers/Biologics/Small molecules (Tocilizumab, Sarilumab, Baricitnib)
3. therapeutic anticoagulation and venous thromboembolism (VTE) prophylaxis
4. colchicine
5. remdesivir[#]
6. lopinavir/ritonavir (Kaletra®)
7. chloroquine or hydroxychloroquine
8. oseltamivir
9. ribavirin and interferon
10. ivermectin[#]
11. ascorbic acid and vitamin D
12. biologics/small molecules (anakinra, baricitinib, ruxolitinib) [#]
13. convalescent plasma[#], intravenous immunoglobulin (IVIG) and monoclonal antibodies/antibody cocktails
14. antibiotics
15. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
16. Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs)
17. SSRIs

[#] 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**) and Angiotensin Converting Enzyme (**ACE**) inhibitors and Angiotensin Receptor Blockers (**ARBs**), 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,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.

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 record 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 both unproven therapies and therapies shown to be efficacious in clinical trials 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 remdesivir 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. Several other trials are in the process of recruiting sites across Canada and are in various stages of ethics and operational approval. The BC Health Authorities are currently reviewing the local feasibility of these clinical studies on a regular basis.

For recommendations pertaining to Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 please visit BCCDC website at:
http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID19_MIS-C_ClinicianGuidance.pdf

For recommendations pertaining to Multisystem Inflammatory Syndrome in Adults (MIS-A) and COVID-19 please visit BCCDC website at:
https://www.cmaj.ca/content/193/25/E956

Assessment

Corticosteroids

Recommendation:

i) Non hospitalized patients with no oxygen requirements:
In adults with mildly ill COVID-19 aged 65 and over OR aged 50 and over with underlying health conditions and within 14 days of symptom onset, inhaled budesonide 800 µg twice daily for 14 days may be considered on a case by case basis in discussion with the patient by clearly highlighting the uncertainty in the benefit of treatment, and the risks and potential adverse effects. Informed consent should be obtained and treatment initiated as soon as possible. Underlying health conditions include weakened immune system due to illness or medication; heart disease and/or hypertension; chronic lung disease; diabetes; hepatic impairment; stroke or other neurological condition; obesity or BMI above 35.

ii) Hospitalized patients requiring oxygen or higher levels of respiratory support
Dexamethasone 6 mg IV/PO q24h for up to 10 days is strongly recommended (RECOVERY trial), unless higher doses are clinically indicated (e.g. asthma exacerbation, refractory septic shock, history of chronic steroid use, obstetric use for fetal lung maturation).
Hydrocortisone 50 mg IV q6h is recommended as an alternative (REMAP-CAP trial). If dexamethasone and hydrocortisone are not available, methylprednisolone 32 mg IV q24h or prednisone 40 mg PO daily are recommended.

Inhaled budesonide

Use of inhaled budesonide was prompted by the noticeable decrease in COVID-19 symptoms in patients with chronic obstructive pulmonary disease. Two trials assessed whether inhaled steroids decreased hospitalization. While both trials are limited by their design and one was stopped early because of enrollment, both demonstrated improvement in self-reported symptom duration, albeit small and not seen with more objective measures. Furthermore, the decrease in hospitalization or medical related visits remains unclear.

Study details:

STOIC: inhaled budesonide in the treatment of early COVID-19

- Design: Open-label, parallel-group, phase 2, RCT
- Inclusion: Adults aged older than 18 years with symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days
- Exclusion: recent use (within 7 days) of inhaled or systemic glucocorticoids or if they had a known allergy or contraindication to inhaled budesonide
- Intervention: usual care or intervention with budesonide dry powder inhaler (Pulmicort Turbuhaler, AstraZeneca, Gothenburg, Sweden) at a dose of 800 µg (two puffs) twice per day
- Outcomes: The primary outcome was defined as COVID-19-related urgent care visits, including emergency department assessment or hospitalisation. Secondary outcomes were clinical recovery, as defined by self-reported time to symptom resolution; viral symptoms measured by

the Common Cold Questionnaire (CCQ)12 and the InFLUenza Patient- Reported Outcome (FLUPro)13 questionnaire; blood oxygen saturations and body temperature; and SARS- CoV-2 viral load.

- Results: 146 participants were randomly assigned—73 to usual care and 73 to budesonide. 139 participants were included in the per-protocol analysis, with 70 participants in the budesonide group and 69 participants in the usual care group (figure 1). 146 participants were included in the ITT analysis, with 73 participants in the budesonide group and 73 participants in the usual care group. Mean age 45; duration of symptoms 3 days before randomization, Median time to symptom resolution 7 days and budesonide taken for median 7 days; PCR+ 94%
- The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment. For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportion 0·123, 95% CI 0·033–0·213; p=0·009). In the per-protocol analysis, the primary outcome occurred in ten (14%) participants in the usual care group and one (1%) participant in budesonide group (difference in proportions 0·131, 95% CI 0·043–0·218; p=0·004), indicating a relative risk reduction of 91% for budesonide. NNT 8.
    - Primary outcome events: 3 participants were symptomatically breathless with oxygen saturations below 94%; one developed diabetic ketoacidosis; one developed acute kidney injury; one had suspected pulmonary embolism; one had suspected rib fractures; three were seen at least twice by an out of hours general practitioner (which included one participant in the budesonide group); and one was seen by a paramedic crew on day 6 and subsequently seen again by a general practitioner on day 8 and sent to the emergency department, where they were directly admitted to the respiratory high dependency unit, requiring continuous positive pressure ventilation for 8 days.
    - Self-reported clinical recovery was 1 day quicker with budesonide compared with usual care (median 7 days [95% CI 6–9] *vs* 8 days [7–11]; log-rank test p=0·007; figure 2)
    - At day 14, self-reported symptoms were present in seven (10%) vs 21 (30%) participants (difference in proportion 0·204, 95% CI 0·075–0·334; p=0·003)
    - Fever in 2% vs 8% and antipyretic use 27 vs 50% (p=0.025)
    - Symptom resolution at 14 days using FLUPro manual 82 vs 72% (NS) and median time to symptom resolution 3 vs 4d (NS)
    - Mean time to recovery 5
    - No difference in days with decreased O2 sats
    - Fever during 14 days 2% vs 8%
    - 5 adverse events all with budesonide (sore throat, dizziness)
- Limitations:
    - Open labelled
    - Trial stopped early due to National Pandemic control measures and therefore didn't reach sample size
    - Young population with few comorbidities

[PRINCIPLE: inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial]

- Design: multicenter, open-label, multi-arm, adaptive platform randomized controlled trial involving people aged ≥65 years, or ≥50 years with comorbidities, and unwell ≤14 days with suspected COVID-19 in the community
- Intervention: randomized to usual care, usual care plus inhaled budesonide (800µg twice daily

for 14 days), or usual care plus other interventions

- Inclusion: >65 or >50 with comorbidities and had ongoing symptoms from polymerase chain reaction (PCR) confirmed or suspected COVID-19 <14days.
- Exclusion: already taking inhaled or systemic corticosteroids, were unable to use an inhaler, or if inhaled budesonide was contraindicated
- Monitoring: online, daily symptom diary for 28 days after randomization, supplemented with telephone calls on days 7, 14 and 28
- Outcomes: co-primary endpoints are time to first self-reported recovery, and hospitalization/death related to COVID-19, both measured over 28 days from randomisation and analysed using Bayesian models
- Results:
    - Trial stopped early by DSMB because accumulating further data to reach pre-specified futility or superiority criteria on hospitalization/death was unlikely due to the successful vaccine rollout and lower than originally anticipated event rate
    - Average age 62.8, Median Day from symptom onset 6, 79.9% took budesonide for at least 7d
    - 2617 (56.1%) tested SARS-CoV-2 positive and contributed data to this interim budesonide primary analysis; 751 budesonide, 1028 usual care and 643 to other interventions.
    - Primary Outcomes:
        - Time to first self-reported recovery was shorter in the budesonide group compared to usual care (hazard ratio 1.208 [95% BCI 1.076 – 1.356], probability of superiority 0.999, estimated benefit [95% BCI] of 3.011 [1.134 – 5.41] days). [significant]
        - Among those in the interim budesonide primary analysis who had the opportunity to contribute data for 28 days follow up, there were 59/692 (8.5%) COVID-19 related hospitalizations/deaths in the budesonide group vs 100/968 (10.3%) in the usual care group (estimated percentage benefit, 2.1% [95% BCI -0.7% – 4.8%], probability of superiority 0.928). [Not significant]
    - Secondary Outcomes:
        - Evidence of benefit with budesonide in the daily score of how well participants felt over 28 days the WHO-5 Wellbeing Index, early sustained recovery, time to sustained recovery. There was no clear evidence of differences in both participants reported or GP reported healthcare services use between groups
- Limitations:
    - Open labelled
    - Patients eligible 38404; not eligible 32096
    - Subjective measures of recovery

Systemic corticosteroids

On June 22, 2020, a preliminary report featuring the results of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was published following a press release. The peer-reviewed manuscript was published one month later in the New England Journal of Medicine. The publication reported the effects of dexamethasone on the outcomes of hospitalized patients with COVID-19; one arm of the pragmatic trial designed to evaluate various therapies simultaneously that can be adapted as the standard of care evolves. The dexamethasone arm of RECOVERY represents the largest trial to-date to not only produce a statistically and clinically significant result, but one that also impacts survival, all by using a well-known, inexpensive treatment. The finding of decreased mortality in the dexamethasone arm has already been touted to be immediately practice changing by the medical community and the media, representing a pivotal advancement in the treatment of COVID-19.

The methodology and results of the dexamethasone arm of RECOVERY have quickly become a topic of debate and critique. Unequivocally, the trial is regarded as high-quality, conducted with transparency and efficiency, and yielding meaningful, indisputable main results. However, any trial subject to a high degree of scrutiny will generate questions and concerns. The points below represent a brief summary and critical appraisal:

Study Details

RECOVERY: dexamethasone in hospitalized patients with COVID-19

- Investigator-initiated, individually randomized, open-label trial of various therapies for COVID-19, compared to standard of care, of which dexamethasone comprised one arm
- Conducted at 176 hospitals in the UK
- 2104 patients were randomly allocated to receive dexamethasone 6mg PO or IV once daily for the duration of their hospital stay or 10 days, whichever was sooner, compared to 4321 patients concurrently allocated to usual care (1:2 randomization)
    - 15% of patients required ventilation, 61% required oxygen and 24% were not receiving any respiratory support at randomization
    - Average age was 66.1 years and 36% patients were female
    - 56% of patients had at least one significant chronic comorbidity such as diabetes, heart disease or kidney disease
    - 82% of patients had a positive laboratory test for SARS-CoV-2
    - Mean duration of therapy was 6 days
- The primary outcome was 28-day mortality from randomization; secondary outcomes included duration of hospital stay and the need for (and duration of) ventilation
- Various subgroup analyses were pre-specified in the detailed protocol for disease severity, time since onset of symptoms, sex and age; however, no p-value adjustment was made for account for multiple comparisons arising from secondary outcomes and subgroup analyses
- An intention-to-treat analysis was set
- In the overall study population, 22.9% of patients randomized to dexamethasone vs. 25.6% patients allocated usual care died within 28 days (adjusted RR 0.83; 95% CI 0.75 to 0.93; P<0.001). The effect increased based on the level of respiratory support received:
    - Invasive mechanical ventilation (29.3% vs. 41.4%, RR 0.64; 95% CI 0.51 to 0.81; p<0.001)
    - Oxygen without invasive mechanical ventilation (23.3% vs. 26.2%, RR 0.82; 95% CI 0.72 to 0.94; p=0.007)
    - Not receiving respiratory support (17.8% vs. 14%, RR 1.19; 95% CI 0.91 to 1.55; p=0.14)

- Patients receiving dexamethasone were more likely to be discharged at 28 days (67.2% vs. 63.5%; HR 1.1 95%CI 1.03-1.17), with a mean length of stay of 12 vs. 13 days, and less likely to progress to mechanical ventilation if not receiving it at baseline (25.6% vs. 27.3%) but the latter was not statistically significant
- Both primary and secondary outcomes were NOT statistically significant in the subgroup without respiratory support at randomization, and driven by patients requiring oxygen and/or mechanical ventilation
- A subgroup analysis based on symptom duration showed that patients with symptoms of <7 days had no statistically significant mortality benefit from dexamethasone; however that was also true for women and those over the age of 70 when subjected to sex and age-based subgroup analyses
- The study concluded that low-dose dexamethasone reduced 28-day mortality among patients hospitalized with COVID-19 receiving invasive mechanical ventilation or oxygen, but not among patients not receiving respiratory support

Study Strengths

There are many noteworthy accomplishments of this trial: follow up was completed in 95% of patients, and 95% of those randomized to dexamethasone received at least one dose. The primary and secondary outcomes are very likely attributable to the steroid as most patients were not receiving other therapies directed at COVID-19 such as lopinavir/ritonavir, hydroxychloroquine or IL-6 inhibitors. Some have stated that ideally, the trial would have been double-blind to minimize bias; however, successfully conducting a trial of this magnitude so quickly would have been hampered by the logistics and resources expanded by the administration of placebos. Regardless, the definitive outcomes such as death, mechanical ventilation or length of stay are less prone to subjective interpretation.

Generalizability to British Columbia Patients

The generalizability of the effect of dexamethasone to patients hospitalized in British Columbia is promising. According to epidemiological summaries, patients in BC hospitals during the peak of the pandemic appeared to be similar in baseline characteristics such as age and comorbidities. The standard of care in UK hospitals parallels that in Canada, minimizing the likelihood of unrecognized systemic confounders. On average, patients in the RECOVERY trial presented 6-13 days after symptom onset, depending on severity, which mirrors experiences in local practice.

One stand out aspect of the RECOVERY trial that has raised questions about its generalizability is the mortality rate in the control arm. A case review of patients admitted to the ICU in Vancouver reported a 15.8% mortality (albeit in-hospital, not 28-day), which is over 2.5 times lower than what was observed in RECOVERY. If the reported relative risk ratio is applied, using dexamethasone in BC under similar circumstances would lead to a 5.5% absolute reduction in mortality, with a NNT closer to 20 instead of 8 for ICU patients. Regardless, a positive result on mortality in the field of critical care is unprecedented and welcomed, even if smaller than in the original trial. In addition, mortality in BC may rise should the system become overwhelmed, which was captured at some centres in the RECOVERY trial.

Study Weaknesses

The largest critique of this part of the RECOVERY trial stems from the nature of the statistical plan, particularly the lack of control for type I error (calling a result statistically significant when it is actually

not), based on multiple comparisons generated by the analyses of subgroups and secondary outcomes.

While it was prespecified in the protocol that no type I error correction would be performed because it would require knowledge of the effect and sample size, the various analyses limited to pairwise univariate comparisons pose a concern of falsely inflating p-values. After all, the more analyses are done, the more likely there will be a statistically significant result and most non-adaptive trials are required to adjust for multiplicity. RECOVERY got a pass mainly because of the technical difficulty of a priori adjustment without knowing how many participants will need to be enrolled, adding arms over time and uneven number of patients in various groups. The primary outcome's p value of <0.001 would likely not change much with adjustment, but this serves as a reminder to only cautiously apply evidence from subgroups and secondary outcomes, even if the p-values are <0.05.

This advice, however, is tempting to ignore when the effect size was profoundly different in patients requiring oxygen or mechanical ventilation vs. those who did not. While the results were reported as not statistically significant, the subgroup not requiring oxygen experienced a 19% *higher* rate of death when given dexamethasone, forcing clinicians to carefully consider who should *not* receive dexamethasone. With many details absent from the manuscript, including timing of randomization with respect to presentation and placement of oxygen, clinical indications for oxygen support, and granular safety endpoints, this decision is difficult to make.

A more careful look at one analysis of the mortality results for the least sick patients reveals a more disconcerting detail - the finding of increased mortality for those not requiring oxygen given dexamethasone is indeed statistically significant if the result is not adjusted for age (RR 1.31 (1.00-1.71); p=0.05), which was the result of the first analyses performed (age-unadjusted Cox regression). The age adjustment was later justified based on a 1.1 year difference between groups even though the statistical plan stated that no statistical tests would be performed for differences in baseline characteristics. Large trials can find small, often clinically unimportant differences in baseline characteristics between groups. If randomization was carried out correctly and chance bias minimized with a large sample size, one may argue that this adjustment was not necessary in RECOVERY. This leads the reader to the possibility that the age adjustment was done based on optics rather than methodological convention and the subsequent analyses using different methods (e.g. One-step vs. Cox regression) were simply looking for the most favourable result. Decreased mortality found in some subgroups that is directly opposed by a simultaneous increase in another is harder to explain, and heterogeneity decreases the impact and validity of the study findings. Even with a sound pathophysiological explanation as to why steroids would be more effective in more severe disease, these findings put into question whether patients not requiring oxygen should receive the recommendation *against* steroids, or be simply left out. We have chosen to do the latter, taking our own advice to very cautiously interpret subgroup analyses in RECOVERY.

Practical Considerations

Overall the study procedures in the RECOVERY trial are described well enough to inform a confident, immediate change in practice for patients requiring oxygen support or mechanical ventilation. Dexamethasone should be initiated at the time of presentation to hospital for those with confirmed or presumed COVID-19 meeting admission criteria. It should be given at a dose of 6mg daily, with oral and IV formulations freely interchangeable, and continued until discharge or for 10 days, whichever is first. Details regarding circumstances that preclude steroid use were not listed in the exclusion criteria of RECOVERY; however it is reasonable to withhold them when serious immediate contraindications are

present. Whether this dexamethasone regimen should be abandoned to another steroid protocol, for example hydrocortisone for refractory septic shock, should be left to the individual treating clinician as patients with a definitive alternative indication for steroids were excluded from the study. Based on the results of this trial, dexamethasone supplies are already on allocation world-wide; whether the same results could be achieved with an alternative steroid is not clear. Methylprednisolone at a dose of 30 mg IV daily, or prednisone 40 mg PO daily would provide the equivalent glucocorticoid/anti-inflammatory effect but yield more mineralocorticoid activity responsible for fluid overload and hypernatremia. Whether this is clinically important in COVID-19 is unknown. The half-life of dexamethasone is 36-54 hours which is about double that of methylprednisolone. In the event of a dexamethasone shortage, slightly longer courses of alternative steroids may be considered. Use of corticosteroids and immunomodulatory medications increases the risk of opportunistic infection reactivation/exacerbation - Strongyloidiasis, tuberculosis, and others. Overall the risk in the context of COVID-19 and with the current dosing strategy is unknown. If risk factors present for Strongyloides (e.g. born in an endemic area, spent 6 months or more in an endemic area; see CATMAT Advisory Committee Statement for full risk assessment guideline), discussion with ID about testing and potential prophylactic Ivermectin should be considered.

METCOVID: methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19

Shortly after the publication of RECOVERY, the results of a smaller randomized controlled trial from Brazil were released. At first glance, it appeared that MetCOVID, a RCT of methylprednisolone in hospitalized patients with COVID-19, contradicted RECOVERY by showing no difference in mortality. However, the critical appraisal below puts the results of this trial into context.

Jeronimo et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (MetCOVID): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial.

- Investigator-led parallel double-blind, placebo-controlled, randomized trial
- Conducted at a single tertiary center in Manaus, Brazil
- 194 patients with confirmed or suspected COVID-19 presenting to hospital were randomized to receive methylprednisolone 0.5mg/kg twice daily for 5 days, or discharge, whichever was sooner, and 199 were randomized to placebo (1:1 randomization)
    - Patients 18 years and older had a SpO_2 of 94% or less on room air or be receiving oxygen (47.5%) or mechanical ventilation (35.4%)
    - Average age was 55, and 34.7% were women
    - Most patients had a co-morbidity including hypertension (48.4%), diabetes (29%) or alcohol use disorder (27.6%).
    - Patients were randomized on average, 13 days from symptom onset.
    - Most patients received 5 days of treatment and methylprednisolone was stopped while still in hospital.
- The primary outcome was 28-day mortality. Various other outcomes were measured, including mortality at 7 and 14 days, length of stay and development of complications (e.g. BOOP).
- The results report a sub-group analysis of those mechanically ventilated, but a sub-group analysis based on age, as discussed in the study results, was not depicted.
- Patients were analyzed in an intention-to-treat fashion
- Overall, for the primary outcome, the 28-day mortality was no different between groups (38.2% vs. 37.1%).

- In a subgroup analysis, those aged >60 experienced a lower mortality with treatment (46.6% vs. 61.9%). Patients over 60 represented 40% of the study population
- Other subgroup analyses were NS, including those requiring mechanical ventilation and those with higher CRPs or SOFA scores.

While the results of MetCOVID put the positive results of RECOVERY into question, the studies have several key differences, one being the sample size and power calculation. MetCOVID's sample was pre-determined and based on a 50% mortality and a 50% absolute mortality reduction, an ARR that is rarely achieved with any treatment. As a comparison, the ARR in recovery was approximately 15%. These practicalities mean that the sample size was far too small in MetCOVID.

Another key difference was the regimen studied. Methylprednisolone has higher mineralocorticoid activity than dexamethasone, leading to more fluid retention and hyperglycemia, as evidenced in MetCOVID. The regimen in RECOVER was also twice as long where most patients received steroids until discharge. Duration of symptoms prior to randomization was also much longer in MetCOVID (13 days), which may be significant in light of RECOVERY's finding that those presenting with more than a week of symptoms do not tend to benefit from steroids.

The generalizability of RECOVERY is higher than MetCOVID when considering patients in British Columbia as the UK health care system bears a closer resemblance to BC than Manaus. The mortality rate in MetCOVID is multiple-fold what was observed in BC at the peak of the pandemic and the majority of patients were nearly 20 years longer than what has been observed in BC hospitals. Thus, the results of MetCOVID do not discredit those in RECOVERY, but rather highlight the importance of the regimen used (dexamethasone preferred), duration of treatment and those who are likely to benefit (those with a shorter duration of symptoms at presentation).

In early September 2020, several publications were simultaneously released in the Journal of the American Medical Association, further characterizing the role of corticosteroids in the treatment of COVID-19. Due to the results of RECOVERY, various RCTs evaluating steroids were stopped; these trials were subsequently combined in a meta-analysis with the following results. Details of the individual trials are expanded further in the critical appraisal below.

WHO Meta-Analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group: Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19 A Meta-analysis

- Prospective meta-analysis that pooled data from 7 ongoing RCTs that evaluated the efficacy of steroids in critically ill patients, including the RECOVERY trial
- While 16 trials were potentially eligible for the prospective meta-analysis, several declined to participate, enrolled no patients or had to placebo. The 7 RCTs that met final eligibility criteria were included.
- RCTs were conducted in 12 countries and data collection ended June 9, 2020

- 678 patients were randomized to receive systemic corticosteroids and compared vs. 1025 patients randomized to placebo
    - Patients received dexamethasone, hydrocortisone and methylprednisolone at various doses and durations. The lowest steroid dose was dexamethasone 6mg/day (RECOVERY) and the highest was dexamethasone 20mg/day (DEXA-COVID and CoDEX)
    - Duration of treatment ranged from 5 to 10 days
- The pre-specified primary outcome was 28-day mortality, calculated using a fixed-effects model, with adverse effects reported as a secondary outcome.
- Overall, 222/678 deaths in the corticosteroid arms, compared to 425/1025 deaths in the placebo arms (OR 0.66 95% CI 0.53-0.82, p<0.001)
- Due to the large sample size and proportion of critically ill patients, 57% of the weight of the meta-analysis came from the RECOVERY trial, followed by 18.7% from CoDEX
- No other trial besides recovery reached statistically significant results alone, likely due to insufficient power. Four of those 6 trials had an OR of less than one, favouring steroid treatment.
- Pre-specified sub-group analyses were also performed and were favourable for most sub-groups, including those receiving mechanical ventilation, receiving supplemental oxygen and regardless of age or symptom onset.
- A comparison of the association of high dose vs. low dose steroids and mortality was imprecise and therefore inconclusive.
- Adverse effects were not statistically significantly associated with steroids in any trial or overall.

Overall, this meta-analysis provides a useful overview and synthesis of evidence supporting the use of steroids in critically ill patients with COVID-19. While largely driven by RECOVERY, the addition of the other 6 RCTs generating similar results is reassuring. The prospective nature of the meta-analysis is also beneficial in determining a pre-defined outcome and minimizing bias. The meta-analysis also provides additional reassurance that steroids should be given to all critically ill patients with COVID-19 regardless of age and symptom onset, something that was unclear in RECOVERY. Unfortunately, the precise agent, dose and duration could not be assessed by the results, but rather confirms that the benefit is likely a class effect.

CAPE-COD: Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19

- Design:
    - Multicenter randomized double-blind sequential trial conducted in France, with interim analyses planned every 50 patients. Trial was embedded in larger CAPECOD trial evaluating hydrocortisone low dose vs placebo in ICU patients on 28-day mortality.
- Inclusion
    - Age >18, PCR+ and 1 of 4 of: MV with PEEP>4, P:F<300 with high flow>50%, Reservoir mask and P:F<300, Pneumonia severity index (PSI) >150
- Intervention
    - Continuous intravenous infusion of hydrocortisone at an initial dose of 200 mg/d or its placebo (saline). Treatment was continued at 200 mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days. If the patient's

respiratory and general status had sufficiently improved by day 4, a short treatment regimen was used (200 mg/d for 4 days, followed by 100 mg/d for 2 days and then 50 mg/d for the next 2 days, for a total of 8 days).

- Baseline
  - Women 22%, Age 63-66, duration of symptoms 9-10d, P:F 130, mechanical vent 80%, Hi-Flow 12%, concomitant therapy 58-64% (most Hydroxychloroquine and azithro)
- Outcomes
  - Treatment failure (death or persistent dependency on mechanical ventilation or high-flow oxygen therapy) on day 21 occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, –8.6% [95.48% CI, –24.9% to 7.7%]; P = .29).
  - Of the 16 patients in each group who did not require invasive mechanical ventilation at baseline, 8 (50%) in the hydrocortisone group and 12 (75%) in the placebo group required subsequent intubation.
  - There was no significant between-group difference in rates of prone positioning; Too few patients were treated with ECMO or inhaled nitric oxide to allow statistical testing. Daily evolution of Pa02:FIO2 ratio during the first week and on days 14 and 21 did not significantly differ
  - Post-hoc at day 21: still vented same, more discharged from ICU in HC group, proportion of death same.
- Limitations
  - Trial terminated early by DMSB after 149pts after release of RECOVERY thereby likely underpowered.
  - Embedded in CAPE-COD trial
  - No data on secondary infections
- Interpretation
  - Low dose hydrocortisone compared with placebo did not reduce treatment failure at 21 days, but trial was likely underpowered.
  - The study was halted early due to the release of the RECOVERY data (see above). The DSMB felt that there was no longer equipoise in relation to the benefits of corticosteroids in COVID-19 disease, therefore the trial stopped after 149 patients of the planned maximum of 290. This trial is therefore likely underpowered. Additionally, the failure rate was initially estimated to be 30% in the control group, with substantial uncertainty at the beginning of the epidemic. The observed rate of the primary outcome in the placebo group was much higher than expected (50.7% cases vs 30.0%). Other limitations include that this trial was embedded within another trial looking at steroids and CAP. Finally, diagnosis of nosocomial infections was not adjudicated; however, the double-blind nature of the trial suggests that the comparison of the rate of secondary infections between the 2 groups may still be valid. The observed difference in the post hoc outcome of proportion of deaths at day 21 was not statistically significant (p=0.06); however, the finding was consistent with the reduced mortality observed with dexamethasone in the subgroup of mechanically ventilated patients from RECOVERY.

Additionally, the meta-analysis by the WHO which included this study showed a mortality benefit with corticosteroids; showing an overall 34% (95%CI 18-47) relative reduction in mortality among critically ill patients with COVID-19 when treated with systemic glucocorticoids compared to either usual care or placebo.

REMAP-CAP: Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19
The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

- Design
  - Ongoing adaptive platform open label in 121 sites in 8 countries
- Inclusion
  - Age >17 with presumed or confirmed COVID and admitted to ICU for respiratory support (invasive or non-invasive with flow >30L/min and FIO>40%) or cardiovascular support (pressors or inotropes)
- Exclusion
  - Death imminent, hypersensitivity to hydrocortisone, systemic steroids needed or >36hrs since ICU admission
- Intervention
  - 1:1:1 - hydrocortisone, 50 mg, every 6 hours for 7 days; intravenous hydrocortisone, 50 mg, every 6 hours while in shock for up to 28 days (stopped when shock resolved or vasopressors stopped); or no hydrocortisone
- Baseline
  - The mean age 59.5 to 60.4 years; male (range, 70.6%-71.5%); body mass index ranged between 29.7 and 30.9; and mechanical ventilation 50.0% and 63.5%
- Outcomes
  - 384 patients (mean age, 60 years; 29% female) randomized to the fixed-dose (n = 137), shock-dependent (n = 146), and no (n = 101) hydrocortisone groups; 379 (99%) completed the study and were included in the analysis. Hydrocortisone given 1-1.2 days after admission; 50-64% on mech ventilation
  - The primary endpoint was organ support–free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days, where patients who died were assigned –1 day. The primary analysis was a bayesian cumulative logistic model that included all patients enrolled with severe COVID-19, adjusting for age, sex, site, region, time, assignment to interventions within other domains, and domain and intervention eligibility. Superiority was defined as the posterior probability of an odds ratio greater than 1 (threshold for trial conclusion of superiority >99%).
  - The median adjusted odds ratio and bayesian probability of superiority were 1.43 (95% credible interval, 0.91-2.27) and 93% for fixed-dose hydrocortisone, respectively, and were 1.22 (95% credible interval, 0.76-1.94) and 80% for shock dependent hydrocortisone compared with no hydrocortisone
- Limitations
  - Open label design
  - 15% of the no steroids group received steroids

    - Trial stopped early due to release of RECOVERY
- Interpretation
    - Compared with no steroids, fixed dose or stress dose hydrocortisone had a 93% and 80% probability of superiority with regards to odds of improved organ free support at 21 days, however trial underpowered.

CoDEX: Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19. The CoDEX Randomized Clinical Trial

- Multicenter, randomized, open-label, clinical trial conducted in 41 ICUs in Brazil
- Patients were included if they were hospitalized with COVID-19 and developed moderate to severe ARDS, according to the Berlin definition
- 151 were randomized to receive 20 mg of dexamethasone IV daily x 5 days followed by 10 mg daily x 5 days, and compared to 148 patients who received standard of care
- The primary outcome was ventilator-free days during the first 28 days
    - 6.6 ventilator free days was observed in those who received dexamethasone vs. 4 days in the standard of care group (difference of 2.26 days, p=0.04)
- The secondary outcomes included all-cause mortality at 28 days, clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death), ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, and Sequential Organ Failure Assessment (SOFA) scores
- There was no significant difference in the pre-specified secondary outcomes of all-cause mortality at 28 days (56.3% vs. 61.5%, p=0.31), ICU-free days during the first 28 days (2.1 vs. 2, p=0.78), mechanical ventilation duration at 28 days (12.5 vs 13.9, p=0.18), or the 6-point ordinal scale at 15 days (5 vs 5).
- Adverse events were not different between groups (21.9% vs 29.1% experienced secondary infections, 31.1% vs 28.3% needed insulin for glucose control, and 3.3% vs 6.1% experienced other serious adverse events.
- The planned sample size of 350 patients was not reached due to the publication of RECOVER
- Despite being stopped early, the study provides additional support for the use of steroids in patients who develop ARDS from COVID-19, further increasing the generalizability for the overarching steroid recommendation. Based on the numerically lower rate of death with an ARR of 5.5%, enrolling 350 patients would not have been sufficiently powered to reach statistical significance either, and RECOVERY continues to lead the way in terms of power.

DEXA-COVID 19

DEXA-COVID 19 is a multicentre, open-label randomized controlled trial involving adult patients with ARDS caused by confirmed SARS-CoV-2 infection admitted to a network of ICUs across Spain. Adult patients with positive reverse-transcriptase polymerase chain reaction on respiratory tract sample, intubated and mechanically ventilated, and have acute onset of moderate-severe ARDS were enrolled. Eligible patients were randomized in a 1:1 ratio to receive dexamethasone plus standard intensive care

or standard intensive care alone. Patients assigned to receive dexamethasone received 20 mg intravenously once daily from day 1 to 5, then 10 mg intravenously once daily from day 6 to 10. This dose was selected based on the authors' previous study of dexamethasone in ARDS. Other therapies such as antivirals, interferon and chloroquine were permitted at the discretion of the attending physician. The primary outcome for this study is all-cause mortality at 60 days from randomization. The secondary outcome is the number of ventilator free days at 28 days. Other outcomes include: ICU mortality, 28-day mortality, duration of mechanical ventilation, length of hospital stay, time to death, viral RNA detection, and safety outcomes. The trial aimed to enroll 200 patients, however, as of September 2, 2020, the trial has been suspended due to lack of enrollment.

DEXA-COVID 19 has not yet been published and preliminary results have been obtained from a meta-analysis on the use of corticosteroids in COVID-19 published by the REACT group. As of June 9, 2020, a total of 19 patients were enrolled, of which, 7 received dexamethasone. Median age was similar 62 (dexamethasone) vs 60, use of vasoactive agents was slightly higher in the control arm (42.9% vs 58.3%), and use of antivirals was similar (86% vs 83%). All patients received hydroxychloroquine. For 28-day mortality, 2 patients in both arms reached the outcome (OR 2 95%CI 0.21-18.69). Three patients in the dexamethasone arm vs 11 patients in the control experienced serious adverse events.

Given the limited recruitment in this study and insufficient details about the enrolled patients, will continue to await publication of this study.

COVID-STEROID

COVID-STEROID is a multicentre, blinded, placebo controlled randomized controlled trial of adult patients with documented COVID-19 receiving at least 10 L/min of oxygen or mechanical ventilation in Denmark. Eligible patients were randomized to receive hydrocortisone 200 mg IV via continuous infusion over 24 hours for 7 days versus normal saline continuous infusion. Both intervention and placebo control were given in addition to standard care. Primary outcome was days alive without life support. Secondary outcomes include: all-cause mortality at day 28, days alive without life support at day 90, all-cause mortality at day 90, serious adverse reactions, days alive and out of hospital at day 90, all-cause mortality at 1 year, and health-related quality of life at 1 year. The trial aimed to randomize 1000 patients, however, as of September 7, 2020, the trial is not recruiting patients.

COVID-STEROID also has not yet been published and preliminary results have been obtained from the meta-analysis on the use of corticosteroids in COVID-19 published by the REACT group. As of June 9, 2020, a total of 29 patients were enrolled, of which, 15 received hydrocortisone. Median age was similar 57 years (hydrocortisone) vs 62 years, 46.7% (hydrocortisone) vs 57.1% were mechanically ventilated at randomization, use of vasoactive agents was similar 33.3% (hydrocortisone) vs 35.7%. Remdesivir was used in 4 placebo control arm patients, and convalescent plasma in 2 placebo control arm patients versus none in the intervention arm. For 28 day mortality, six patients in the hydrocortisone arm versus 2 patients in the control arm reached the outcome (OR 4 95%CI 0.65-24.66). One patient receiving hydrocortisone versus none in the control arm experienced serious adverse events.

Given the limited recruitment in this study and insufficient details about the enrolled patients, will continue to await publication of this study.

Older Studies

Prior to the publication of the dexamethasone arm of RECOVERY, the medical community was divided on its recommendation for the use of corticosteroids in patients with COVID-19, and their recommendations have not all been updated. Most recommendations focused on the small proportion of COVID-19 patients with acute respiratory distress syndrome (ARDS), as this is where evidence for steroids overlaps. 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 in March 2020. In May, a Canadian Guideline was published echoing this sentiment. 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, although this is likely to change. While evidence in concerning this therapeutic area has been largely overshadowed by the RECOVERY trial, the publications that historically informed practice are worth mentioning.

COVID-19 and ARDS

A single observational study by Wu et al, 2020 comprises the only evidence that directly addresses the question of steroid use in COVID-19 and ARDS. While generally considered as being of low quality due to the study design and lack of adjustment for confounding factors, the study was published in early March in JAMA and is still widely referenced, being the only applicable publication on this topic. The study looked at risk factors of 201 patients with COVID 19 in Wuhan, China, of who 84 (41.8%) developed ARDS. The study reported that patients with ARDS were more likely to be older, have coagulopathy, certain clinical symptoms and various comorbidities. The study performed innumerable bivariate analyses, one of which was of the relationship between methylprednisolone and death, stratified by the presence of ARDS. Among the patients with ARDS, of those who received methylprednisolone treatment, 23 of 50 (46.0%) died, while of those who did not receive methylprednisolone treatment, 21 of 34 (61.8%) died. This analysis was not conducted for those without ARDS. The study concluded that there was a large, statistically significant association between corticosteroid and lower mortality (HR 0.38 95% CI 0.20 to 0.72) in those 84 patients. However, due to the significant methodological issues, including confounding, this result gained little credibility among the medical community and did not change practice.

Various other studies and meta-analyses provide indirect evidence for the use of corticosteroids in pneumonia caused by bacteria and viruses such as influenza and coronaviruses MERS and SARS that are sometimes applied to COVID 19. This includes a very recent Canadian meta-analysis in July 2020 by Ye et al., which informed the rationale for the above-mentioned COVID-19 Canadian Guideline titled "Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline". The Ye et al. meta-analysis, concluded that based on evidence from 851 patients with non-COVID 19 ARDS in 7 RCTs, the use of corticosteroids resulted in a reduction in mortality of 17.3%

(95% CI −27.8% to −4.3%). However, the meta-analysis stated that the evidence was very poor quality, and subsequently the guideline citing it referred to the recommendation to give steroids for patients with COVID-19 and ARDS as a "weak recommendation of low quality evidence". One reassuring finding of the Ye et al. publication was that corticosteroid use in this population did not lead to an increased risk of gastrointestinal bleeding and neuromuscular weakness, and only a very modest increase in serum glucose (~8%).

The authors of the Surviving Sepsis Campaign Guidelines also came to similar conclusions regarding steroids and non-COVID 19 ARDS:

"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)."

COVID-19 without ARDS

Besides the RECOVERY trial, data for the use of corticosteroids for patients with COVID-19 without ARDS is extremely limited. One published but not peer-reviewed observational report of 26 patients with severe COVID-19 stated that the use of methylprednisolone 1-2mg/kg/day for 5-7 days was associated with a shorter duration of oxygen use (8.2 days vs. 13.5 days; $p<0.0001$), along with improved radiographic findings. However, this study has significant risk of bias and lacks details that would allow for an appropriate critical appraisal (Wang 2020).

The Surviving Sepsis Campaign Guidelines also comment on the use of corticosteroids in viral pneumonia, and stated that the effects were not clear in patients with non-COVID 19 coronavirus:

"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)."

COVID 19 Viral Shedding

Two observational studies have shown that corticosteroids may increase viral shedding in COVID 19.

One study from China by Xu et al. looked at 113 patients, 64 of whom received steroids. Of those 64, most patients (n=46) were found to exhibit positive viral PCR at ≥15 days, whereas only 15 patients

cleared the virus in the first two weeks, a statistically significant difference. In the abstract, the study concluded that steroids are associated with a longer viral shedding time. However, multivariable analyses of factors associated with the duration of SARS-CoV-2 virus RNA detection depicted in Table 2 of the publication showed that receipt of corticosteroids was not statistically significantly linked to viral shedding (OR 1.38 95% CI 0.52-3.65, p=0.519).

Another Chinese study designed to look at risk factors associated with viral shedding by Yan et al. analyzed 120 patients hospitalized with COVID 19. The primary outcome of the study was to assess the impact of lopinavir/ritonavir on viral shedding; however, other variables were also studied though a multivariate logistic regression analysis. The results, which were not peer-reviewed, reported that the mean duration of viral shedding was 23 days, and that corticosteroid treatment of a dose equivalent of 25mg or more of methylprednisolone per day was NOT associated with prolonged viral shedding. Corticosteroids were given to 45% of patients and their receipt had no impact on the presence of the virus in two consecutive tests of cure (OR=0.80 95% CI 0.38-1.70; p=0.57).

It is biologically explainable that those with prolonged and severe illness have longer viral shedding; however, those who are severely ill are more likely to receive steroids in non-randomized trials. Analyses of steroids as an independent variable in SARS-CoV-2 RNA detection are lacking, and the clinical implications are not well understood. In viral non-COVID pneumonia (e.g. MERS) in the ICU, several observational studies showed an increase in viral shedding with corticosteroid use (Arabi 2018, Hui 2018, Lee 2004), potentially indicating viral replication. However, significant methodological issues exist in these studies; for example, the OR for the association was statistically significant in some, but not all statistical analyses. Furthermore, the clinical consequences of increased viral shedding is uncertain and the generalizability to COVID 19 is not clear.

IL-6 blockers/Biologics/Small molecules (Tocilizumab, Sarilumab, Baricitnib)

Recommendation:
Tocilizumab 400mg IV (single dose) or sarilumab 400mg IV (single dose) is recommended (REMAP-CAP and RECOVERY) for patients requiring life support due to confirmed COVID-19. This includes high-flow oxygen support (e.g., Optiflow) if flow rate > 30 L/min and FiO2 > 0.4 OR invasive or non-invasive ventilation OR vasopressor or inotropic support. Tocilizumab or sarilumab must be administered within 24 hours of the initiation of life support measures. Patients admitted to hospital for more than 14 days with symptoms of COVID-19 should not receive tocilizumab or sarilumab for this indication. Tocilizumab or sarilumab should only be initiated when life support is required because of COVID-19 rather than other causes (such as bacterial infection, pulmonary embolism, etc.).

If tocilizumab is not available due to ongoing global shortages, baricitinib is recommended as an alternative.

Baricitinib 4 mg po daily (for patients with GFR ≥ 60 mL/min) or 2 mg po daily (for patients with GFR 30-59 mL/min) or 2 mg po every 2nd day (for patients with GFR 15-29 mL/min) up to 14 days, or until discharge from hospital (whichever occurs first) is recommended (COV-BARRIER) for patients requiring life support due to confirmed COVID-19. This includes high-flow oxygen support (e.g., Optiflow) if flow rate > 30 L/min and FiO2 > 0.4 OR invasive or non-invasive ventilation OR vasopressor or inotropic support. Baricitinib should be administered within 24 hours of the initiation of life support measures. Baricitinib should only be initiated when life support is required because of COVID rather than other causes (such as bacterial infection, pulmonary embolism, etc). Baricitinib should not be administered to patients with neutrophils < 1.0 giga/L, lymphocytes < 0.2 giga/L, ALT or AST > 5 x ULN, or eGFR < 15 mL/min (or receiving renal replacement therapy).

*There are very limited data on baricitinib in pregnancy. Risks and benefits of baricitinib should be discussed on a case by case basis with pregnant women with severe COVID-19.

Tocilizumab is **not** recommended for patients receiving low-flow oxygen support. The RECOVERY trial found a survival benefit of 4% (tocilizumab 29% vs. usual care 33% 28-day mortality) in patients who had CRP ≥75 mg/L AND low-flow oxygen, non-invasive respiratory support, or invasive mechanical ventilation. However, considering the scarcity of IL-6 blockers in Canada, drug therapy should be prioritized to the persons with both the highest need and the greatest likelihood of benefiting from the therapy. Combined with outstanding issues in the preliminary findings of the RECOVERY trial (e.g. 17% of patients randomized to tocilizumab not receiving the drug), the CTC recommends prioritizing tocilizumab use only for critically ill patients at this time, which is the population shown to benefit in both the REMAP and RECOVERY trials.

Tocilizumab is an interleukin-6 (IL-6) monoclonal antibody used as immunotherapy for treatment of rheumatoid arthritis. Sarilumab is a humanized monoclonal antibody targeted towards the IL-6 receptor and used for the same condition. Anakinra is an IL-1 receptor antagonist.

Initial interest in cytokine blockade started when a small case series from Wuhan, China was published in a non-peer reviewed Chinese website Chinaxiv.org and subsequently in the Proceedings of the National Academy of Sciences (Xu 2020). Twenty 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 r was unknown.

Subsequently, several studies demonstrated that inflammation, as measured by CRP or IL-6, were associated with progression to respiratory failure or death (Herold 2020, Laguna-Goya 2020). Several randomized clinical trials were initiated.

On January 7, 2021, a pre-print (now published NEJM April 22nd) for the REMAP-CAP reported that IL-6 blockade with tocilizumab or sarilumab improved outcomes, including survival, in critically ill COVID-19 patients. In this randomized controlled trial, 353 patients were assigned to tocilizumab (8 mg/kg IV up to a maximum of 800 mg), 48 to sarilumab (400 mg IV fixed dose) and 402 to control. The primary outcome was an ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21. Relative to control, the median adjusted odds ratios were 1.64 (95% credible intervals [CrI] 1.25, 2.14) for tocilizumab and 1.76 (95%CrI 1.17,2.91) for sarilumab. Hospital mortality was 28% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control. The number needed to treat to prevent in hospital mortality for tocilizumab was 13. All secondary outcomes supported efficacy of tocilizumab and sarilumab and there was no increase in serious adverse events in the IL-6 blockade treated patients.

On February 11, 2021, a pre-print (now published JAMA May 1st) for the RECOVERY trial (**doi:** https://doi.org/10.1101/2021.02.11.21249258) reported that tocilizumab improves outcomes for hospitalized patients with hypoxemia (SaO2 < 92% on room air) and systemic inflammation, C-reactive protein > 75 mg/L. This multi-center trial randomized patients meeting these criteria to tocilizumab dosed by body weight (8 mg/kg if < 40 kg, 400 mg if > 40 and =< 65 kg, 600 mg if > 65 and =< 90 kg, 800 mg if > 90 kg) versus standard care in a 1:1 ratio. Between April 23, 2020 and Jan 24, 2021, 4116 adults were randomized. 596 (29%) of the 2022 patients allocated to tocilizumab and 694 (33%) of the patient allocated to usual care died within 28 days (rate ratio 0.86; 95% confidence interval 0.77-0.96; p=0.007).

Earlier randomized clinical trials in hospitalized but non-critically ill patients were negative or showed small potentially beneficial effects for tocilizumab. Five large randomized controlled clinical trials of tocilizumab for COVID-19 have been reported in pre-print or peer-reviewed publication. COVACTA was a Hoffmann-Roche sponsored multicentre, double-blind, placebo-controlled clinical trial in patients with severe COVID-19. 452 patients were randomized. There was no difference in clinical status or mortality at day 28 between the placebo and tocilizumab arms. Final publications of this trial are still pending. EMPACTA was a Genentech sponsored trial for patients with severe COVID-19 pneumonia who were not mechanically ventilated at the time of enrollment. Sites enrolling high-risk and minority patients were encouraged and approximately 50% of patients in both arms were Hispanic/Latino, 15% Black/African American and 12% American Indian/Alaska Native. The primary outcome of a combination of death or

mechanical ventilation by day 28 was significant -- 12.0% (8.52% to 16.86%) vs. 19.3 % (13.34% to 27.36%) for the tocilizumab and placebo arms, respectively (log-rank P=0.0360; hazard ratio, 0.56 [95% CI, 0.33 to 0.97]). However, all-cause mortality by day 28 was not statistically significantly different -- 10.4% vs. 8.6% for tocilizumab vs. placebo, respectively (weighted difference, 2.0% [95% CI, – 5.2% to 7.8%]).

The smaller CORIMUNO trial was an investigator-initiated, open-label RCT of tocilizumab vs. standard-of-care, that enrolled at 9 hospitals in France in early April. The study failed to meet its primary endpoint, which was a composite of progression to a score of 5 or higher on the WHO-CPS at day 4 (- 9.0% [−21.0 to 3.1] and survival without need for mechanical ventilation at day 14 (HR 0.58 [0.30 to 1.09]). There was an improvement in the secondary composite endpoint of high-flow oxygen, non- invasive ventilation, mechanical ventilation, or death at the 90% confidence level (0.58 with 90% CrI of 0.33-1.00).

Two RCTs selected patients for hyperinflammation; both were negative. The Roche sponsored American BACC Bay Tocilizumab Trial randomized 243 patients in a 2:1 ratio to tocilizumab or placebo. Patients with hyperinflammation such as CRP > 50 mg/L or ferritin > 500 ug/L not yet intubated were eligible. The primary outcome was intubation or death. At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had worsening of disease. The Italian RCT-TCZ-COVID-19 Study group randomized 126 patients in a 1:1 ratio to tocilizumab or placebo. Patients with an inflammatory phenotype (fever, CRP > 100 mg/L, etc.) were eligible. The primary endpoint was admission to ICU or requirement for mechanical ventilation and 28.3% of the patients in the tocilizumab arm and 27% of patients in the standard care group showed clinical worsening.

Further information on long term outcomes is expected from these trials.

REMDACTA is the last large sponsored clinical trial enrolling, which is a randomized double-blind, placebo-controlled trial of tocilizumab vs. placebo in patients with severe COVID-19 getting 10 days of remdesivir (NCT 04409262). It is also sponsored by Hoffmann-Roche.

Sarilumab was also studied in an industry (Sanofi) sponsored phase 2 /3 multicenter randomized controlled trial (https://www.sciencedirect.com/science/article/pii/S2213260021000990). Between Mar 28 and Jul 3, 2020, 420 patients were randomized; 416 patients received treatment (84 placebo, 159 sariliumab 200 mg IV, 173 sarilumab 400 mg IV). The primary endpoint was time to ≥ 2 point clinical improvement on a 7 point ordinal scale (1, death, to 7, not hospitalized). There was no significant difference in median time to ≥ 2 point improvement between placebo (12 days, 9-15), sarilumab 200 mg (10 days, 9-12) or sarilumab 400 (10 days, 9-13), p=0.34). There was a non-significant difference in survival at day 29 between sarilumab 400 mg (88%) compared to placebo (79%, p=0.25) in critically ill patients, who comprised 38.9% (162/416) of the study population.

A Cochrane rapid review confirmed the day 28 mortality of benefit for tocilizumab, RR 0.89 (95% CI 0.82-0.97). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013881/full

Due to increased global demand, Roche announced a tier 3 shortage of tocilizumab in Canada in March 2021. In this context, the BC CTC recommends fixed dose 400 mg IV tocilizumab for the following reasons:

1) Low dose steroids are sufficient to reduce mortality in COVID-19 (e.g. 6 mg/day of dexamethasone).

2) Tocilizumab is dosed 4 mg/kg IV in rheumatoid arthritis; this dose provides a maximum concentration of 88 ug/mL (https://pubmed.ncbi.nlm.nih.gov/24255004/).
3) Serum IL-6 levels in COVID-19 are typically 20-200 pg/mL and sIL-6 receptor levels are 40-60 ng/mL (https://www.cell.com/cell-reports-medicine/pdf/S2666-3791(21)00019-7.pdf); thus the Cmax achieved by tocilizumab 4 mg/kg (i.e. 400 mg or less for adults < 100 kg) is orders of magnitude higher than needed to saturate the trans signaling system.
4) Low dose tocilizumab has similar effects on fever, CRP and other markers of inflammation in retrospective COVID-19 studies. https://pubmed.ncbi.nlm.nih.gov/32405160/ ; 1) https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2117

Therefore, on April 9, 2021 the CTC recommended fixed dose tocilizumab 400 mg IV OR sarilumab 400 mg IV x 1 dose in patients meeting REMAP-CAP criteria (Optiflow 0.4 or higher level of support).

THIS SECTION IS CURRENTLY UNDER CONSTRUCTION

To date, randomized controlled trials investigating the use of anakinra, baricitinib or ruxolitinib have not provided compelling evidence for recommendation in the treatment of COVID-19.

Perhaps the most notable trial investigating these agents is the ACTT-2 trial which compared baricitinib plus remdesivir versus remdesivir alone in hospitalized adults with COVID-19. This was a double-blinded, randomized, placebo-controlled trial of 1033 patients evaluating baricitinib plus remdesivir in hospitalized adults with moderate or severe COVID-19. Moderate disease was defined as ordinal score of 4 or 5 (not receiving ventilation) and severe disease defined as ordinal score 6 or 7 (non-invasive or invasive ventilation). Patients were diagnosed by a nasopharyngeal swab and a randomized in a 1:1 fashion to receive either remdesivir 200 mg IV on day 1, followed by 100 mg daily of days 2 through 10 or until hospital discharge or death and baricitinib 4 mg po/ng for 14 days or until hospital discharge or death (n=515) OR remdesivir and placebo (n=518). Primary endpoint was time to recovery, during the 28 days after enrollment, with recovery defined as achieving category 1, 2 or 3 on the eight-category ordinal scale stratified according to baseline disease severity. Analysis of data was based on an intention to treat. No adjustments were made for multiplicity. 706 patients had moderate disease and 327 patients with severe disease. Median age was 55.4 years and 63.1% were male. For the primary outcome, patients who received combination treatment recovered 1 day faster (7 days vs 8 days) than patients who received remdesivir and placebo (CI 1.01 to 1.32; p=0.03). The median time to recovery among patients receiving non-invasive ventilation or high-flow oxygen (baseline ordinal score of 6) was 10 days in the combo group and 18 days in the control group (CI 1.10 to 2.08). For patients with ordinal score of 4, 5 and 7 the differences were not significant. A secondary outcome of odds of improvement in clinical status at day 15 as assessed with the ordinal scale was greater in the combination group than in the control group (1.3, CI 1.0 to 1.6). Patients with a baseline ordinal score of 6 who received combo treatment were most likely to have clinical improvement at day 15 (OR 2.2, CI 1.4 to 3.6). Mortality was 5.1% in the combination group and 7.8% in the control group (not statistically significant).

The primary limitation of applying the ACTT-2 trial in a British Columbia context is that it was performed prior to widespread utilization of dexamethasone (with only 10% of trial participants receiving corticosteroids). Additionally, remdesivir was standard of care in this trial and this is not the case in British Columbia. Finally, tocilizumab is now recommended in British Columbia for critically ill patients requiring high flow oxygen support or vasopressors. It is not possible to interpret the potential benefit of adding baricitinib on clinical outcomes for patients treated with steroids and tocilizumab as standard of care.

Therapeutic Anticoagulation and Venous Thromboembolism (VTE) Prophylaxis

Recommendation:
i) Hospitalized patients requiring low-flow oxygen:
Therapeutic anticoagulation (LMWH preferred) may be beneficial and therefore considered in patients without high risk features* for serious bleeding and NOT requiring organ support. If used, anticoagulation for COVID-19 should start within 72 hours of admission and continue for 14 days or until hospital discharge. Patients who decompensate and require organ support while on therapeutic anticoagulation should continue on therapeutic anticoagulation. Therapeutic anticoagulation was superior to standard of care for composite 21-day organ support free survival in the ATTACC/ACTIV-4a/REMAP-CAP trials. Benefits appear to be driven by reducing progression to high-flow oxygen, non-invasive ventilation, or vasopressors. There was insufficient certainty on whether therapeutic anticoagulation improves mortality or intubation. Therapeutic anticoagulation reduces thrombotic events (1.4% vs 2.7%) but may increase major bleeding (1.9% vs 0.9%). *High risk features for bleeding include: age 75 or greater, eGFR less than 30 mL/min, any coagulopathy, platelet count less than 50, use of dual antiplatelet therapy, recent history of serious GI bleed or recent intracranial condition (stroke, neurosurgery, aneurysm, cancer), epidural or spinal catheter.

ii) Hospitalized patients requiring organ support (high-flow oxygen, non-invasive ventilation, mechanical ventilation and/or vasopressor/inotropic support)
Prophylactic-intensity dosing of low molecular weight heparin (LMWH) is recommended for VTE prophylaxis in patients who do not have suspected or confirmed VTE (or other indications for therapeutic anticoagulation). There is a high probability of harm when therapeutic anticoagulation is initiated in patients who have received organ support for greater than 48 hours (n=1074; NIH mpRCT). **Patients receiving therapeutic anticoagulation** for COVID-19 **prior** to organ support should **REMAIN** on therapeutic anticoagulation and continue for up to 14 days or until hospital discharge.

Evidence used for these recommendations
The multiplatform RCT (ATTACC, ACTIV-4a & REMAP-CAP) was designed to determine if therapeutic anticoagulation is superior to usual care anticoagulant prophylaxis in treating patients hospitalized for COVID-19. Interim pre-publication data were released on January 28, 2021 (https://www.attacc.org/presentations). Results of the critical care group were later released in preprint on March 12, 2021. More recent data of the group not requiring organ support were published in a pre-print on May 17, 2021 (Berger et al.) **A critical appraisal of these data, along with the recently published ACTION and RAPID trial are under way.**

In the critically ill COVID-19 patients (those requiring organ support at enrollment), therapeutic anticoagulation met the pre-defined criteria for FUTILITY with respect to 21-day mortality and organ support compared with usual care (aOR 0.87; 95% credible interval (CrI) 0.70-1.08; posterior probability of futility 99.8%). No improvement in hospital survival was seen (64.3% therapeutic vs 65.3% usual care; aOR 0.88; 95% CrI 0.67-1.16). Major bleeding was more common with therapeutic anticoagulation (3.1% vs 2.4%; aOR 1.19; 95% CrI 0.57-2.49).

The CTC will continue to update the "Clinical Practice Guidance for Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19" document based on any new studies and relevant data. Please refer to the BCCDC website for the most updated information: http://www.bccdc.ca/Health-Professionals-Site/Documents/Antimicrobial-Immunomodulatory-Therapy-adults.pdf

VTE Prophylaxis

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 May 18, 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).

Recently, a Canadian trial led by St. Michael's Hospital has been designed to evaluate the optimal prophylactic regimen in non-ICU COVID-19 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 two times the upper limit of normal. The primary objective of the study is to evaluate whether full-dose, therapeutic anticoagulation with LMWH or UFH in those with laboratory risk factors can prevent the development of critical illness, VTE and reduce mortality.

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 mcg/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.

Poissy 2020-04-24: A case series in one French hospital of 107 patients admitted to the ICU for COVID-19.

- The cumulative rate of PE in patients was 20.4% (95% CI 13.1 to 28.7%) at day 15 of ICU admission.
- At the time of PE diagnosis, 20 of 22 patients were receiving prophylactic anticoagulation with either UFH or LMWH according to current guidelines and 2 of the 22 patients were receiving therapeutic anticoagulation for prior VTE and atrial fibrillation.
- By comparison, the authors matched cohorts from the same time interval in the previous year and one from concurrent patients with influenza rather than COVID-19 and the incidence of PE were 6% and 8% respectively.
- This study supports many others that suggest that VTE rates in critically-ill COVID-19 patients are higher than in those with non-COVID viral pneumonia.

Paranjpe 2020-05-05: A retrospective study of 2,733 patients with confirmed COVID-19 admitted to five New York City hospitals.

- 786 (28%) patients received therapeutic dose anticoagulation during their hospital course. The indication for therapeutic anticoagulation was not specified.
- Anticoagulated patients were more likely to require mechanical ventilation (29.8% vs 8.1% p<0.001) and 395 (14.4%) of patients were intubated and critically ill.
- Treatment with therapeutic anticoagulation was associated with a reduced risk of mortality with a HR 0.86 (95% CI 0.82-0.89)
- Bleeding was reported in 1.9% of patients not treated with anticoagulation vs. 3% in patients treated with therapeutic anticoagulation (p=0.2)
- Bleeding was more common among patients intubated 30/395 (7.5%) vs non-intubated patients 32/2378 (1.35%).
- While this study suggests that therapeutic anticoagulation may be of benefit, little can be drawn from these conclusions due to the weak study methodology. For example, it is unknown as to why patients were administered full-dose anticoagulation, and whether those in the comparator group also had indications for treatment. There were significant differences between groups which were not considered or adjusted for. In addition, the study did not comment on the significance of the higher bleeding risk in intubated patients.
- One commentary by Delanger-Patersen also pointed that the survival analysis is subject to an "immortal time bias" based on how the authors attributed T0 to those that were anticoagulated. T0 was the date of admission for those not anticoagulated and the start of anticoagulation for

those in the treatment group. Since Initiation of anticoagulation was delayed by on average 5 days, the authors introduced "immortal person-time" among anticoagulation users thereby conferring an artificial survival advantage to the treatment group. This bias is also referred to as survivor treatment selection bias and can occur in survival analyses where patients who live longer are more likely to receive treatment than patients who suffer an early death. The results by Paranjpe et al. give the false illusion of improved survival among anticoagulation users when in fact ~25% anticoagulated patients were not at risk of death until after day 5 and all non-users were at risk from day 0.

Trigonis 2020-06-26: retrospective case series of a single center hospital in Indiana, USA of 45 patients admitted to the ICU for COVID-19

- included patients who required mechanical ventilation and were ordered lower extremity ultrasonography for detection of VTE
- mean age 60, BMI 34, 1 day from admission to intubation, 7 days from admission to ultrasonography
- all patients received pharmacologic prophylaxis and choice of prophylaxis did not affect rate of VTE; regimens included LMWH 40 mg q24h, LMWH 30 mg q12h, LMWH 40 mg q12h, UFH 5000 units q8h, and UFH 7500 units q8h
- 19/45 (42.2%) had DVT and these were detected after median 6 days (IQR 4 to 8 days) from admission
- D-dimers on date of ultrasonography was 5606 mg/L and 2274 mg/L in patients with and without DVTs, respectively
- authors suggested using D-dimer cutoff 2000 mg/L to trigger ultrasonography and 5500 mg/L to trigger empiric full anticoagulation based on sensitivity and specificity values
- limitations of this study included its retrospective nature, small sample size, and lack of standard prophylaxis doses; in addition, because only those patients who received ultrasonography were included, the overall rate of DVT found in this study likely overpredicts the rate of DVT for all critically ill patients with COVID-19

Parzy 2020-06-26: retrospective case series of a single center hospital in France of 13 patients on VV ECMO with COVID-19

- included patients with COVID-19 placed on VV ECMO and had a thoraco-abdominopelvic CT scan performed after decannulation
- compared COVID-19 patients to historic ECMO patients with influenza and bacterial pneumonia
- median days on ECMO was 10 (IQR 8 to 13)
- all patients were started on heparin infusions with anti-Xa heparin levels with target 0.3 to 0.6 units/mL (mean measured 0.41)
- all 13 patients experienced VTEs: 10/13 (76.9%) had isolated cannula-associated DVT, 2/13 (15.4%) had isolated PE, and 1/13 (7.7%) had both cannula-associated DVT and PE
- 7 patients had jugular DVTs, 10 patients had femoral DVTs, and 6 patients had both sites with DVTs
- 1 patient had thrombotic occlusion of the ECMO pump and 1 patient had oxygenator thrombosis, and 4 patients required circuit replacements
- numerically higher rates of cannula-associated DVTs in COVID-19 patients vs influenza patients

With the exception of a few trials, 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 occurred 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.

Post-discharge

While there are currently no studies specific to COVID-19 that evaluate the efficacy and safety of ongoing VTE prophylaxis post-discharge, two landmark trials are worth mentioning to round out the discussion. Both these studies preceded COVID-19; however they included patients with generalizable characteristics such as elevated D-dimers, infection and respiratory failure.

In 2016, the APEX trial (Cohen et. al) randomized 7513 patients hospitalized with acute medical illness to receive enoxaparin 40 mg once daily for 10±4 days plus oral betrixaban placebo for 35 to 42 days or enoxaparin placebo for 10±4 days plus oral betrixaban 80 mg daily for 35 to 42 days. The study employed an atypical statistical analysis plan where three pre-specified, progressively inclusive cohorts were subsequently analyzed if no difference was found in the preceding analysis: patients with an elevated D-dimer level (cohort 1), then patients with an elevated D-dimer level or an age of at least 75 years (cohort 2), and finally all the enrolled patients (overall population cohort). The primary outcome of asymptomatic and symptomatic VTE or VTE-related death did not reach statistical significance in cohort 1 (6.9% in betrixaban group vs. 8.5% in enoxaparin group; p=0.054); however it was statistically significant for cohort 2 (5.6% vs. 7.1% p=0.03) and in the general population (5.3% vs. 7% p=0.0006). This difference was likely due to increased power from increasing inclusion as cohort 1 consisted of only 3870 of the

7513 patients in the overall population. A frequent critique of the study is that asymptomatic DVT comprised the majority of events, and that while a difference in major bleeding was not observed, bleeding rates were higher in the betrixaban groups if clinically relevant non-major bleeding was added (3.2% vs. 1.7% p<0.001). This study led to FDA approval of betrixaban for VTE prophylaxis in the US, but not in other countries.

Following APEX, a second trial (MARINER) evaluating post-discharge prophylaxis was published in 2018. In this study, 12 024 hospitalized patients with an increased VTE risk were randomized to 45 days of rivaroxaban 10 mg daily or placebo following discharge. Patients received standard LMWH VTE prophylaxis during the index hospitalization, which lasted 3-10 days. There was no difference in the primary outcome of symptomatic VTE or VTE-mortality between groups (rivaroxaban 0.83% vs. 1.10%; p=0.14) and the study was stopped early due to futility. Major bleeding rates were similar. There was a reduction in symptomatic VTE with rivaroxaban (HR 0.44; 95% CI 0.22-0.89) though there were only 36 symptomatic thrombi among the >12,000 participants. The NNT to prevent one symptomatic VTE was 546. The findings of MARINER suggest that post-discharge provision of rivaroxaban for 45 days is of limited utility among medical patients at increased risk for VTE. The population included in this study parallels that of APEX: patients were on average 70 years old and most had elevated D-dimers. While this information is not specified in the APEX trial, about half of patients in the MARINER study had an encounter in the ICU.

While no direct comparisons have been made, patients with COVID-19 admitted to medical wards appear to have a symptomatic VTE rate similar to patients without COVID-19 (~1%). However, it is probable that patients with COVID-19 initially admitted to the ICU and discharged to the ward are at an increased VTE risk, and that the MARINER trial likely underestimates the benefit of continued anticoagulation despite including patients with a previous critical care admission. However, at this time the precise benefit vs. risk of post-discharge VTE prophylaxis in the setting of COVID-19 is unknown, and various issues such as lack of outpatient coverage for these agents pose barriers to routine implementation of this evidence.

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 mcg/mL vs. 0.6 mcg/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 >2 mcg/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 (e.g.: 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.

Colchicine

Recommendation:
In patients aged 40 years or older with PCR-confirmed COVID-19 who have at least one risk factor† and no contraindications††, colchicine 0.6 mg PO BID x 3 days, then 0.6 mg daily x 27 days may be considered on a case-by-case basis in discussion with the patient by clearly highlighting the uncertainty in the benefit of treatment, and the risks and potential adverse effects. Informed consent should be obtained and treatment initiated as soon as possible.

†Age ≥70 years, obesity (BMI ≥30 kg/m^2), diabetes, hypertension (systolic ≥150 mmHg), respiratory or coronary disease, heart failure, fever ≥38.4°C, and dyspnea.

†† Contraindications – GFR <30 mL/min, inflammatory bowel disease, chronic diarrhea or malabsorption, neuromuscular disease, severe liver disease, chemotherapy, current colchicine treatment, hypersensitivity to colchicine, or concurrent medications that interact with colchicine (e.g. amiodarone, azoles, carvedilol, cyclosporine, estradiol, macrolides, propafenone, protease inhibitors, quinidine, quinine, verapamil).

Human Data:
In the COLCORONA randomized, double-blind, placebo-controlled trial of non-hospitalized patients with probable or proven COVID-19, colchicine 0.5 mg PO BID x 3 days, then 0.5 mg daily x 27 days was not statistically significant in reducing the composite primary endpoint of hospitalization or mortality at 30 days when compared to placebo **(4.7% colchicine [n=2235] vs. 5.8% placebo [n=2253]; OR 0.79; 95% CI 0.61 to 1.03; p<0.08)**. However, when only COVID-19-confirmed patients were included, results were statistically significant **(4.6% colchicine [n=2075] vs. 6.0% placebo [n=2084]; OR 0.75; 95% CI 0.57 to 0.99; p<0.04)**. Of these patients, the odds ratio was statistically significant for reduction in hospitalization 0.75 (95%CI, 0.57 to 0.99), but not for mechanical ventilation 0.50 (95%CI, 0.23 to 1.07) and death 0.56 (95%CI, 0.19 to 1.66). Serious adverse events were 4.9% in colchicine vs. 6.3% in placebo groups (p=0.05), pneumonia 2.9% vs. 4.1% (p=0.02), pulmonary embolism 0.5% vs. 0.1% (p=0.01), and diarrhea 13.7% vs. 7.3% (p<0.0001). The authors concluded that in non-hospitalized patients with COVID-19, colchicine reduces the composite of rate of death or hospitalization. However, several limitations exist. The intent-to-treat analysis did not show statistical significance in the primary endpoint, yet after removal of 329 patients without PCR-confirmed COVID-19 significance was observed. The absolute difference of 1.4% for the primary endpoint provides a relatively minor benefit corresponding to a number-needed-to-treat of 71, and odds ratios had wide confidence intervals. Median age was young at 54.7 years with only 9.9% who were 70 years or older. Additionally, the trial was terminated early due to logistical issues and intent for early publication, attaining 4506 out of the intended sample of 6000 patients. Based on these findings, the CTC does not recommend the routine use of colchicine for treatment of outpatients with COVID-19.

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 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 2020)

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

(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).

Remdesivir

Recommendation:
Remdesivir has not demonstrated benefit in survival, progression to ventilation or length of hospital stay and remains uncertain with respect to shortening time to recovery by 5 days. The World Health Organization (WHO) has issued a conditional recommendation against the use of remdesivir in hospitalized COVID-19 patients. Further evaluation in approved clinical trials is strongly encouraged. If remdesivir is used outside of clinical trials, full disclosure of risks and benefits with consideration of patient values and preferences are necessary, as it is not considered standard of care. Furthermore, it should be restricted to hospitalized patients requiring supplemental oxygen but not requiring non-invasive or invasive mechanical ventilation.

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).

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 22, 2020, preliminary results from the NIAID RCT were published demonstrating a faster time to recovery in patients receiving remdesivir compared to those who received placebo (11 vs 15 days $p<0.001$). May 27, 2020 WHO interim guidance on clinical management of COVID-19 continued to recommend remdesivir only in the context of a clinical trial. The final publication of the ACTT-1 study continued to demonstrate a faster time to clinical recovery. Subgroup analysis showed that this benefit was only seen in the population requiring low flow supplemental oxygen and was not demonstrated in either those not requiring supplemental oxygen or those requiring high flow supplemental oxygen, non-invasive and invasive mechanical ventilation or ECMO. Secondary analysis of mortality benefit was not found in ACTT-1. On October 15, 2020, the preprint of the SOLIDARITY trial was released. In this study of over 5000 participants randomized to remdesivir versus open label standard of care, there was no benefit for in-hospital mortality or progression to mechanical ventilation.

Remdesivir received conditional approval by Health Canada for the treatment of COVID-19 on July 28, 2020. Remdesivir is being allocated by Health Canada to individual provinces based on the local epidemiology and case burden. It is at the discretion of individual provinces to allocate the medication. It was previously available as compassionate use via Health Canada's Special Access Program for individual case-by-case applications. Given the lack of demonstrated survival benefit and the significant cost of this novel therapy, an analysis of cost-effectiveness of remdesivir is underway by CADTH.

BC COVID-19 Therapeutics Committee continues to recommend against the use of remdesivir outside of approved clinical trials. Remdesivir may be beneficial in reducing the time to clinical recovery as shown in the ACTT-1 trial however no mortality benefit has been demonstrated in this study or the much larger

Solidarity trial. Due to the potential for benefit in certain subgroups and remaining equipoise, the CTC continues to recommend enrollment in clinical trials of remdesivir.

The Remdesivir Review and Advisory Working Group (RRAWG) is comprised of representatives from multiple provincial committees including the BC Pharmacy Emergency Operation Center (EOC), the BC CTC, the Critical Care Services Executive Committee, the Provincial Antimicrobial Clinical Expert Group and the Provincial Healthcare Ethics Advisory Team. Given the recent surge in COVID-19 cases and rising hospitalizations along with allocation of Health Canada procured supply of remdesivir, on November 10, 2020, the decision from this group was that Remdesivir may be considered for the treatment of COVID-19 in hospitalized patients requiring supplemental oxygen but not requiring nov-invasive mechanical ventilation, invasive mechanical ventilation or ECMO. Remdesivir should not be prescribed if CrCl <30 mL/min or ALT >5xULN. If prescribed, the recommended dosing of Remdesivir is 200 mg IV load on day one followed by 100 mg IV daily for 4 more days or until hospital discharge, whichever comes first. In patients still requiring supplemental oxygen on day 5 of therapy, remdesivir may be continued for up to a maximum of 10 days.

Human Data

Pan 10-15-20

- Pre-print of Solidarity trial; Open-label, randomized trial of remdesivir, hydroxychloroquine, lopinavir, interferon-beta-1a compared to standard of care. Inclusion of meta-analysis of available trials assessing remdesivir.
- Primary outcome of in-hospital mortality. Secondary outcomes of initiation of ventilation and hospital length of stay.
- Analysis of remdesivir (n=2743) vs standard of care (n=2708) demonstrated rate ratio for 28-day in-hospital mortality of 0.95 (95% CI 0.81-1.11).
- Initiation of ventilation was no different between remdesivir and standard of care arms (295 vs 284).
- Meta-analysis of four available trials found death rate ratio of 0.91 (95% CI 0.79-1.05) for remdesivir vs control. There is a trend to favorable outcome with remdesivir in the lower risk, non-ventilated groups (RR 0.8, 95% CI 0.63-1.01).

Beigel 10-08-2020

- Final report of the ACTT-1 trial; Randomized, double-blinded, placebo-controlled trial of remdesivir versus placebo, see below (n=1062).
- Patients treated with remdesivir had a shorter time to recovery, defined as reaching categorization 1-3 on the ordinal scale, compared to placebo (10 days vs 15 days p<0.001)
- Several subgroup analyses were performed. The greatest benefit in time to recovery was demonstrated in those with ordinal scale 5 (on supplemental oxygen, not requiring high-flow or ventilation). No benefit was seen in those not requiring supplemental oxygen or in those on high-flow oxygen or requiring mechanical ventilation at baseline. Benefit was demonstrated in those randomized within the first 10 days from symptom onset but not in those randomized beyond 10 days from symptom onset.
- Mortality was a secondary outcome. There was a trend to improved day 29 mortality in the remdesivir treatment arm (HR 0.73, 95% CI 0.52-1.03). Again the greatest benefit was seen in the subgroup with ordinal scale 5 at baseline (HR 0.3, 95% CI 0.14-0.64).

Spinner 08-21-2020

- Randomized, open label study comparing standard of care to 5 vs 10 days of remdesivir.
- 584 patients with moderate COVID infection included.
- Moderate COVID defined as confirmed infiltrates on chest X-ray but not requiring supplemental oxygen with room air oxygen saturations of >94%.
- Primary outcome was day 11 status on 7-point ordinal scale. The 5 day remdesivir arm had an OR of 1.65 for improved day 11 status compared to standard of care. As per authors, this finding is of uncertain clinical importance. There was no difference in all cause mortality between all three groups.
- There were a greater number of adverse events in the 10 day remdesivir arm compared to standard of care.
- The standard of care group was more likely to receive other candidate therapeutics including hydroxychloroquine, azithromycin and lopinavir/ritonavir.

Olender 07-24-2020

- Comparative analysis of interim data from two separate cohorts, one cohort from a prospective trial of patients all receiving remdesivir and one retrospective cohort of patients not receiving remdesivir.
- Primary endpoint recovery at day 14 defined as improvement on ordinal scale.
- More patients in the remdesivir cohort reached the primary endpoint compared to the retrospective cohort. The secondary endpoint of day 14 mortality was reached in 7.6% of the remdesivir treated cohort and 12.5% of the non-remdesivir treated cohort.
- This paper continues to demonstrate trends in remdesivir benefit but the methods used make the utility of this current analysis limited and do not provide any greater information beyond ACTT-1. The retrospective cohort was collected as much as 1 month before the remdesivir cohort and the critical care management of COVID-19 patients likely evolved in this time period.

Goldman 05-27-2020

- Randomized, open label trial of 397 patients, comparing 5 versus 10 days of remdesivir in hospitalized patients with COVID-19 from March 6 to 26, 2020.
- Conducted in the United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea and Taiwan.
- Included hospitalized patients greater than 12 years old, with confirmed SARS-CoV-2 infection, with an SpO2 below 94% on room air or requiring supplemental oxygen and radiographic evidence of pulmonary infiltrates. Patients were excluded if they were receiving mechanical ventilation, ECMO, had an ALT or AST >5 x ULN, CrCl <50 ml per minute or were receiving other candidate antiviral therapy.
- At baseline after randomization, the patients in the 10-day treatment arm were sicker with greater supplemental oxygen needs.
- Primary endpoint was clinical status on day 14 assessed on a 7-point ordinal scale with 65% of patients in the 5 day arm showing clinical improvement compared to 54% in the 10 day arm. Despite randomization, given the baseline differences in the arms, adjustment for baseline clinical status were performed and showed no difference in clinical status between the two arms (p=0.14).
- Mortality was numerically lower in the 5-day arm compared to the 10-day arm (8% vs 11%).
- Although limited by the lack of a placebo controlled arm, this study demonstrates that there was no significant difference in clinical status at day 14 in patients treated with 5 versus 10 days of

remdesivir. This suggests that if adopted into clinical use, 5 days may be the preferred treatment taking into account resource allocation implications.

Beigel 05-22-2020

- Randomized, double-blinded, placebo-controlled trial of remdesivir versus placebo
- Conducted in the USA, Denmark, Germany, Greece, Spain, United Kingdom, South Korea, Singapore, Mexico, Japan.
- 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 or ECMO; excluded those with ALT/AST 5 times above ULN, GFR below 30, or pregnant/breastfeeding. Patients were allowed to receive additional treatments for COVID-19 per individual institutional policies.
- Randomization was stratified by center and disease severity
- Primary outcome was changed to time to recovery defined as the first day a patient was either discharged from hospital or hospitalized for only infection control purposes.
- Trial was stopped early on April 27, 2020 after DSMB review and participants were unblinded and placebo patients could receive remdesivir if clinically indicated.
- 1063 patients were randomized in a 1:1 fashion to remdesivir or placebo. At trial cessation, 391 remdesivir arm patients and 340 placebo arm patients had completed day 29 follow up, recovered or died. 301 patients had not recovered or completed day 29 follow up at analysis.
- Median time to recovery was significantly shorter for the remdesivir arm compared to placebo (11 vs 15 days $p<0.001$) and hazard ratio for mortality trended to lower for remdesivir HR 0.7 (CI 0.47-1.04) however day 28 mortality was not available. In a subgroup analysis when stratified by baseline oxygen requirement, there was no difference between remdesivir and placebo in either the mild/moderate patients not requiring oxygen at baseline or the critical patients requiring high flow oxygen or mechanical ventilation. Benefit appeared to be derived by the cohort requiring oxygen but not yet critically ill.

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, errors in statistical analysis, 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.

Lopinavir/Ritonavir (Kaletra®)

Recommendation:
Lopinavir/ritonavir is not recommended for treatment of COVID-19. Lopinavir/ritonavir is not recommended for prophylaxis of COVID-19 outside of approved randomized-controlled trials.

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

RECOVERY 05/10/2020: Open label RCT in UK evaluating various therapies for COVID-19 in hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection

- 1616 patients randomized to receive Lpv/r 400/100 mg PO q12h x 10 days or discharge (if sooner) vs 3424 patients received usual care. Median duration of Lpv/r treatment was 5 days.
- Independent data monitoring committee reviewed unblinded data and found no beneficial effect. Enrollment was therefore closed on June 29, 2020.
- No significant difference seen in 28-day mortality; 23% (Lpv/r) vs 22% (standard care), RR 1.03 95%CI 0.91-1.17, p=0.6. No differences seen in risk of progression to mechanical ventilation or length of hospital stay
- No differences seen in rate of cardiac arrhythmias between groups. One report of serious adverse effect attributed to Lpv/r: elevated alanine aminotransferase that resolved after stopping treatment.

WHO SOLIDARITY 15/10/2020: Multi-country open label adaptive RCT evaluating various therapies in adult patients hospitalized with COVID-19 (currently available only in non-peer reviewed form)

- Of 11266 eligible patients, 1411 patients were randomized to receive Lpv/r 400/100 mg PO q12h for 14 days. Due to use of tablet formulation, patients who were ventilated and unable to swallow did not receive drug.
- Relative risk for in-hospital mortality with Lpv/r: 1.00 (95% CI 0.79-1.25, p=0.97). Pre-planned analyses of patients not ventilated on study entry, did not demonstrate a protective effect of Lpv/r.
- Lopinavir arm was discontinued July 4, 2020 for futility.

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 mcg/mL. However, when combined with ribavirin, lopinavir appears considerably more effective (with an inhibitory concentration of 1 mcg/mL) (Chu 2004).
- For reference, the peak and trough serum concentrations of lopinavir are 10 and 5.5 mcg/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.

Chloroquine and Hydroxychloroquine

Recommendation:
Chloroquine or hydroxychloroquine (with or without azithromycin) is not recommended for treatment or prophylaxis of COVID-19.

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.

Unfortunately, due to the over-exaggeration of benefits of hydroxychloroquine for treatment of COVID-19 in early observational studies, there has been early widespread adoption of its off-label use. This resulted in drug supply chain issues both in Canada and worldwide and placed undue strain on patients with established indications for hydroxychloroquine such as rheumatoid arthritis. Additionally, 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.

When 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.

Human Data
Hydroxychloroquine has been studied in a variety of patient settings to test its efficacy for both prevention and treatment of COVID-19. Consistently across all studies, hydroxychloroquine has not demonstrated clinically significant benefits. Specifically, published RCTs that have tested hydroxychloroquine in pre-exposure prophylaxis, post-exposure prophylaxis, infected non-hospitalized patients not requiring oxygen, or hospitalized patients requiring oxygen have not demonstrated efficacy of hydroxychloroquine over either standard of care or placebo.

On June 5, 2020, the United Kingdom's NHS sponsored RECOVERY trial authors published a press release announcing that in hospitalized patients with COVID-19, hydroxychloroquine did not improve mortality. They evaluated 1542 patients who received hydroxychloroquine versus 3132 patients who received standard of care alone. There were no differences in 28-day mortality (25.7% vs 23.5%, HR 1.11 (95%CI 0.98 to 1.26), p = 0.10). There were also no differences in hospital length of stay or other clinical outcomes. Due to these preliminary findings, the RECOVERY trial has stopped recruiting patients into its hydroxychloroquine arm.

Subsequently, on June 17, 2020 and June 20, 2020, the WHO's SOLIDARITY trial authors and the NIH's ORCHID study authors, respectively, have released similar announcements for their hydroxychloroquine

treatment arms for hospitalized patients with COVID-19. Specifically, the SOLIDARITY study group stopped its hydroxychloroquine arm due to news release from the UK RECOVERY trial and from its own data including the French DISCOVERY trial. The ORCHID study group announced that after randomizing 470 patients (out of a total planned 500 patients) in their placebo-controlled study, preliminary results showed no additional benefit using hydroxychloroquine for treatment of COVID-19 in hospitalized patients.

There has been an extraordinary amount of observational data published to investigate associations between use of hydroxychloroquine and clinical outcomes. It is important to note that observational studies should be viewed as hypothesis-generating and that causality is rarely demonstrated. To date, no well-performed large observational studies have shown strong associations of clinical benefit with hydroxychloroquine and some in fact provide low certainty signals of possible cardiac related harms when using hydroxychloroquine to treat COVID-19.

A detailed description of all fully published randomized clinical trials and observational studies are provided below.

Randomized clinical trials

Rajasingham (COVID PREP) 2020-09-21

- design
    - medrxiv publication - non-peer reviewed (NCT04328467)
    - randomized, allocation-concealed, double-blind, placebo-controlled trial of 1483 **healthcare workers at high-risk of exposure (pre-exposure prophylaxis)**
    - healthcare workers in ED, ICU, covid-19 wards, and first responders
    - North American study organized from the Minnesota group (same as Boulware and Skipper study above)
    - Apr 6 to May 26, 2020
    - power calculation: assumed 10% event rate over 12 weeks, 50% relative risk reduction with intervention, 80% power, needed 1050 participants per arm
- inclusion
    - healthcare workers (ED, ICU, covid ward, or first responder) including physicians, nurses, advanced care providers, respiratory therapists
    - 18 years or older
    - exposure risk to persons with covid-19
- exclusion
    - active or prior covid-1 infection
    - no expected exposure to patients
    - contraindication to hcq
- interventions
    - hcq 400 mg bid x 1 day then 400 mg once weekly x 12 weeks (n=494)
        - median hcq blood conc = 98 ng/mL
    - hcq 400 mg bid x 1 day then 400 mg twice weekly x 12 weeks (n=495)
        - median hcq blood conc = 200 ng/mL
    - matching placebo (n=494)
- baseline
    - age 51; female 51%; white 85%; no comorbidities 66%; HTN 14%; asthma 10%
    - emergency department 41%; ICU 18%; OR 12%; covid wards 10%; first responder 9%

        - more than 14 hours direct contact per week 91% of participants
        - AGMP performed by 79% of participants
        - interacted with covid-19 patients while not wearing mask or face shield 14%
- outcomes
    - primary: time to confirmed or probable covid-19-compatible illness (probably disease defined as cough, SOB, dyspnea or two or more of fever, chills, rigors, myalgia, headache, sore throat, new olfactory or taste disorders) - cases were adjudicated by 3 blinded ID physicians
        - hcq once weekly: 0.27 events per person-years (5.9% overall)
            - HR 0.72 (0.44 to 1.16, p=0.18 vs placebo)
        - hcq twice weekly: 0.28 events per person-years (5.9% overall)
            - HR 0.74 (0.46 to 1.19, p=0.22 vs placebo)
        - placebo: 0.38 events per person-years (7.9% overall)
        - combined hcq vs placebo
            - HR 0.73 (0.48 to 1.09, p=0.12)
    - secondary
        - hospitalization
            - once weekly 3 patients, twice weekly 8 patients, placebo 9 patients
        - adverse events
            - hcq once weekly 31%, twice weekly 36%, placebo 21%; p<0.001
            - most common GI upset
            - no differences in serious adverse events
        - no differences in HCQ concentrations between those who with probable or confirmed covid infection vs those without covid infection in those taking hcq
- limitations
    - did not meet power calculation (needed 3150 participants in total) due to low recruitment rate; recruitment severely limited by FDA reports of QT prolongation and arrhythmias with hcq two weeks after trial started
    - did not study higher doses than once or twice weekly dosing regimens
    - lack of available PCR testing meant only 18% of diagnosed infection were confirmed PCR positive
- interpretation
    - randomized double-blinded trial did not show benefit with use of hydroxychloroquine at 400 mg once or twice weekly as pre-exposure prophylaxis in high risk health care workers for prevention of covid-19 infection
    - due to the study no meeting power, if the absolute risk reduction of 0.11 events per person-years is real, then 9 high-risk healthcare workers would need to take hcq for one year to prevent 1 covid-19 case; benefit would be even less for healthcare workers at lower risk settings

Mitja 2020-07-26

- design
    - cluster randomized open-label multi-center trial in 2314 **asymptomatic contacts exposed to known COVID-19 cases** (672) in Spain
    - cluster randomization via clusters of healthy individuals epidemiologically linked to a positive covid case (entire cluster randomized to treatment or control)
    - Mar 17 to Apr 28, 2020

    - power needed 2850 patients for 90% to detect 10% difference in incidence with expected incidence of 15% in control arm
- inclusion
    - age over 18
    - recent history of close contact exposure to PCR-confirmed covid case (i.e., more than 15 minutes within 2 meters, up to 7 days before study enrolment)
    - absence of covid symptoms in 2 weeks prior to enrolment
    - healthcare worker, household contact, nursing home worker, nursing home resident
- exclusion
- interventions
    - HCQ 800 mg x 1, then 400 mg daily x 6 days (n=1116)
    - standard of care (n=1198)
- baseline
    - age 49; female 73%; PCR test negative at baseline 88%; median exposure to enrolment 4 days; size of clusters per group 2; HCW 60%; household contacts 28%; nursing home residents 12%; CVD 12%; resp disease 5%; use of masks at time of exposure 66%;
- outcomes
    - primary
        - PCR-confirmed symptomatic COVID-19 at day 14
            - 5.7% vs 6.2%, RR 0.89, 95% CI 0.54 to 1.46
    - secondary
        - symptomatic or PCR-confirmed COVID-19 infection
            - 18.7% vs 17.8%, RR 1.04, 95% CI 0.77 to 1.41
        - hospitalizations for covid
        - treatment emergent AE: 51.6% vs 5.9%
            - GI (nausea, diarrhea, abdo pain), CNS (drowsy, headache, metallic taste)
        - SAE: no differences
- limitations
    - open label design
- interpretation
    - in this large open-label study, use of HCQ in otherwise healthy asymptomatic patients with exposure to known covid index cases did not reduce rates of PCR-positive clinical infection with covid; there were substantially more minor GI and CNS adverse events with HCQ use

Cavalcanti 2020-07-23

- design
    - randomized, open-label clinical trial of 667 **hospitalized patients with minimal oxygen requirements** (504 with confirmed covid-19) at 55 hospital sites in Brazil
    -
- inclusion
    - 18 years or older
    - hospitalized with suspected or confirmed covid-19
    - 14 days or less since symptom onset
- exclusion
    - oxygen supplementation more than 4 litres per minute
    - oxygen supplementation via high flow nasal cannula or invasive or non-invasive ventilation

    - use of hydroxychloroquine or macrolide in previous 24 hours
    - history of severe ventricular tachycardia or ECG findings of QTc above 480 msec
- interventions
    - hcq 400 mg bid + azithro 500 mg daily x 7 days (n=217)
    - hcq 400 mg bid x 7 days (n=221)
    - standard of care (n=227)
- baseline
    - age 50; male 58%; HTN 40%; DM 19%; smokers 7%; obese 15%; COPD 2%; baseline receiving oxygen 42%; time from symptom onset randomization 7 days (IQR 5 to 9 days)
- outcomes
    - primary: proportional odds of having higher score on a 7-level ordinal scale of overall clinical status (higher scores indicating worse condition) at day 15 in patients with confirmed covid-19 infection
        - hcq vs SoC: OR 1.21 (95% CI 0.69 to 2.11, p=1.00)
        - hcq + azithro vs SOC: OR 0.99 (95% CI 0.57 to 1.73), p=1.00)
    - number of days free from respiratory support within 15 days
        - 11.1 vs 11.2. vs 11.1 days
    - in hospital death
        - 2.9% vs 4.4% vs 3.5%
    - QT prolongation over 480 msec
        - 14.7% vs 14.6% vs 1.7%
    - liver enzyme ALT/AST increase
        - 10.9% vs 8.5% vs 3.4%
- limitations
    - 504 patients out of 665 randomized patients included in primary outcome analysis as the primary outcome was modified to evaluate only those patients with confirmed covid-19 infections
    - open label design
- interpretation
    - in hospitalized patients treated at 7 days after symptom onset, there were no clinical benefits with use of hydroxychloroquine with or without azithromycin compared to standard of care
    - there were notably more events of QTc prolongation with patients who received hydroxychloroquine compared to those who did not receive it

Mitja 2020-07-16

- design
    - randomized, allocation concealed, open-label, multi-center clinical trial in 293 **non-hospitalized patients** in Spain between Mar 17 and May 26, 2020
    - 28-day follow-up
    - 60 (8%) of original randomized patients LTFU as missing PCR tests or withdrawal of consent
    - power: 280 patients for 80% power to detect 0.5 log reduction at two sided p=0.05
- inclusion
    - non-hospitalized
    - mild symptoms (fever, cough, SOB, anosmia)
    - adults over 18 years old
    - SARS-CoV-2 PCR test confirmed

    - symptoms less than 5 days
- exclusion
    - moderate to severe covid req hospitalization
    - mental instability
    - known allergy to study drug
    - known retinal or severe liver or renal disease
    - history cardiac arrhythmias or QT prolongation
    - psoriasis
    - known HIV infection
    - pregnant
- interventions
    - HCQ 800 mg on day 1, then 400 mg daily x 6 days (n=136)
    - Standard of care (n=157)
- baseline
    - age 42; female 69%; 87% health care workers; viral load 7.9 log copies/mL; median symptom onset to randomization 3 days; CVD 10%; resp disease 6%; viral load at baseline 8 log 10 copies per mL
- outcomes
    - primary
        - viral RNA load in npx swabs up to 7 days after treatment start
            - day 3: -1.41 copies vs -1.41 copies, difference 0.01, 95% CI -0.28 to 0.29
            - day 7: -3.44 copies vs -3.37 copies, difference 0.07, 95% CI -0.44 to 0.29
    - secondary
        - hospitalization: 5.9% vs 7.1%, RR 0.75, 95% CI 0.32 to 1.77
        - time from randomization to resolution symptoms: 10 vs 12 days, p = 0.38
        - mechanical ventilation: no events
        - deaths: no events
        - any adverse event: 72% vs 8.7% (most frequent diarrhea, nausea, abdo pain, drowsiness, headache, metallic taste)
        - SAE: no differences
- limitations
    - open label design
- interpretation
    - reasonably well conducted open-label RCT showed no viriologic nor clinical symptoms benefits with using HCQ vs standard of care in otherwise healthy adult outpatients with COVID-19 after an average of 3 days of symptoms

Skipper 2020-07-16

- design
    - randomized, allocation concealed, double-blinded, placebo-controlled clinical trial of 491 **symptomatic non-hospitalized patients** at sites across USA and Canada [sister trial of study by Boulware above - same NCT number]
    - Mar 22 to May 20
    - conducted study via emails, internet surveys, and medication deliveries
- inclusion
    - non-hospitalized adults with less than 4 days of symptoms
    - PCR confirmed covid-19 or exposure to known covid-19 person
- exclusion

    - symptoms > 4 days, age < 18, current hospitalization, allergy, retinal eye disease, known G6PD deficiency, known CKD stage IV or V, known porphyria, weight < 40 kg, on chemotherapy, use of flecainide, amiodarone, digoxin, procainamide, or sotalol, known structural heart disease, history prolonged QTc, on QTc prolonging medications
- interventions
    - hcq 800 mg x 1 dose, then 600 mg in 6-8 hours, then 600 mg daily x 4 more days
    - placebo
- baseline
    - lab confirmed SARS-CoV-2 or exposure to known SARS-CoV-2 person 81%; enrolled within 1 day of symptoms 56%; Canadian 8%; age 41; weight 73 kg; women 53%; white 48%; smoker 4%; health care worker 57%; household contacts = 18%; no comorbidities 70%; HTN 10%; DM 4%
- outcomes
    - ***initial outcome was ordinal scale of not hospitalized, hospitalized, or ICU - but due to very low hospitalization rate, changed primary outcome to symptom scale***
    - primary: change in overall symptom score at day 14 based on 0-10 scale with no symptoms = 0 and most severe symptoms = 10 (death = 10)
        - hcq 2.60 point reduction, vs placebo 2.33 point reduction, difference -0.27 points (95% CI difference -0.61 to 0.07 points, p=0.117)
    - symptoms at day 14
        - hcq 49/201 (24%) vs placebo 59/194 (30%), p=0.21
    - medication adverse events
        - hcq 92/212 (43%) vs placebo 46/211 (22%), p<0.001
            - GI symptoms most commonly
            - no serious adverse events documented
    - no differences in hospitalizations or deaths (total incidence of both combined was 15/165 (3.2%))
    - no differences in subgroup with PCR-confirmed disease
- limitations
    - reasonably well designed RCT in view of limitations of running a trial during a pandemic
    - only 58% participants had SARS-CoV-2 testing due to testing limitations in US
- interpretation
    - hcq was not associated with reduction of symptoms in non-hospitalized symptomatic participants with covid-19 with less than 4 days of symptoms

Horby (RECOVERY) 2020-07-15

- design
    - medrxiv non-peer reviewed
    - randomized, open-label, adaptive platform trial from 176 hospitals in UK assessing 4716 **hospitalized patients with varying levels of oxygen support**
    - part of an adaptive study that studied multiple interventions versus standard of care
        - hydroxychloroquine, dexamethasone, and lopinavir/ritonavir now stopped
        - azithromycin, tocilizumab, and convalescent plasma ongoing as of this publication
- inclusion
    - hospitalized patients with clinically suspected or lab confirmed covid-19 infection
    - age > 18
- exclusion

    - known QTc prolongation
- interventions
    - hydroxychloroquine 800 mg at zero and six hours, then 400 mg q12h x 9 days or until discharge (n=1561)
    - standard of care (n=3155)
- baseline
    - age 65; male 62%; days from symptom onset 9; days since hospitalization 3; no oxygen required 23%; supplemental oxygen 60%; mech vent 17%; DM 27%; heart disease 25%; lung disease 21%; CKD 7%; SARS-CoV-2 positive 90%
- outcomes
    - primary: death at day 28
        - hcq 418/1561 (26.8%) vs SoC 788/3155 (25.0%), RR 1.09 (95% CI 0.96 to 1.23, p=0.18)
    - discharged from hospital alive within 28 days
        - hcq 941/1561 (60.3%) vs SoC 1982/3155 (62.8%), RR 0.92 (95% CI 0.85 to 0.99)
    - receipt of mechanical ventilation or death
        - hcq 388/1300 (29.8%) vs SoC 696/2623 (26.5%), RR 1.12 (95% CI 1.01 to 1.25)
    - no differences detected in cardiac arrhythmias
    - no significant findings in subgroup analyses
- limitations
    - open label design
- interpretation
    - in hospitalized patients with COVID-19, hcq was not associated with reduced mortality, but was associated with increased hospital length of stay and progression towards mechanical ventilation or death

Boulware 2020-06-03

- design
    - randomized, allocation concealed, double-blinded, placebo-controlled clinical trial of 821 **asymptomatic participants with known COVID-19 exposure** at sites across USA and Canada
    - trial Mar 17 to
    - participant self-enrollment via RedCap
    - original power calculation 1500 pts required for 50% relative risk reduction of estimated 10% event rate with placebo; second interim analysis reduced required sample size to 956 due to higher-than-expected event rate in control group; third interim analysis decided to stop trial due to futility
- inclusion
    - known COVID-19 exposure (voluntary report) to a person with lab-confirmed COVID-19 (household or occupational)
    - distance less than 6 feet for 10 minutes while wearing neither a face mask or eye shield (high risk) or while only wearing face mask (moderate risk)
    - within 3 or 4 days of exposure (trial procedure adjusted 1 week into trial)
- exclusion
    - age below 18
    - hospitalized
    - symptoms of COVID-19 or PCR-proven SARS-CoV-2
    - allergy to study medication, G6PD deficiency

    - CKD (stage 4 or 5), porphyria, weight below 40 kg, on chemotherapy
    - current user of HCQ, azithromycin, or anti-arrhythmics
        - macrolides, quinolones, azoles
        - TCAs, SSRIs, NDRIs, SNRIs, anti-psychotics, methadone, triptans
    - known prolonged QT interval
    - medications associated with ventricular arrhythmias, cardiac death, or QT prolongation
    - ischemic heart disease, structural heart disease
- interventions
    - HCQ 800 mg x 1, then 600 mg 6 to 8 hours later, than 600 mg daily x 4 more days (total course 5 days) (n=414)
        - dose was selected to achieve concentrations above EC50 = 0.72 mcmol/L
    - placebo matching folate tablets (n=407)
- baseline
    - age 40; women 52%; white 60%; no comorbidities 72%; HTN 12%; DM 3%; asthma 8%; current smoker 3%; 68% taking no regular meds; HCW 66%; high risk exposure 88%; Canada 2.5%, USA 97%
- outcomes
    - measured at day 14 after enrollment
    - symptomatic illness confirmed by PCR or COVID-19 symptoms if testing unavailable
        - confirmed cases = positive PCR test
        - probable cases = cough, SOB, or two or more of fever, chills, rigors, myalgia, headache, sore throat, olfactory/taste disorders)
        - possible cases = one of symptoms above or diarrhea
        - ***all require epidemiologic linkage; cases confirmed by panel of 4 ID physicians
        - HCQ 48/414 (11.8%) vs placebo 58/407 (14.3%), difference -2.4%, 95% CI -7.0 to 2.2%, p = 0.35
        - only 16/113 (14%) symptomatic cases were confirmed with PCR testing
    - hospitalization
        - 1 hospitalization in each group
    - deaths
        - no deaths in each group
    - adherence to trial medication
        - HCQ 312/414 (75.4%) vs placebo 336/407 (82.6%), p = 0.01
    - symptoms at day 14 for those who developed symptoms
        - no difference
    - adverse events
        - no arrhythmias
        - any side effects
            - HCQ 140/349 (40.1%) vs placebo 59/351 (16.8%), p < 0.001
            - difference mostly GI side effects including nausea, upset stomach, diarrhea, abdo discomfort, vomiting
        - vision changes in 1% of HCQ group, none in placebo group
    - sensitivity analysis
        - same findings when accounting for lost to follow-up participants (approx 10% all participants) -
        - same findings with per-protocol analysis
        - same findings when excluding “possible covid-19” cases
    - subgroups analysis

        - no differences in time of starting prophylaxis relative to exposure
        - no differences in type of exposure, sex, age
- limitations
    - relatively young healthy sample where majority had no comorbidities
    - HCQ: 47% correctly guessed HCQ, 44% unsure, 10% placebo
    - placebo: 36% correctly guessed placebo, 48% unsure, 17% HCQ
    - relies on participant voluntary information; may not have seen any healthcare provider to confirm symptoms
    - only 14% of symptomatic cases were confirmed by PCR
- interpretation
    - well performed RCT showed no significant differences in contracting covid-19 with prophylactic HCQ in asymptomatic participants with known covid-19 exposure within 96 hours
    - no apparent differences in serious adverse events, hospitalizations, arrhythmias in a relatively healthy population with few to no comorbidities
    - high incidence of GI related side effects (40% vs 17%) with HCQ
    - while potential benefits of HCQ in an older population with more comorbidities cannot be ruled out, there could also be more potential adverse events in such a population

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

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

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

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; the clinical endpoints in this study were of questionable relevance and the magnitude of benefit shown, if any, was not impressive

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

Observational studies

Arshad 2020-07-01

- observational cohort multicenter study in 2541 patients at 6 hospitals (Henry Ford Health System (HFHS)) in Michigan
- Cox-proportional hazards model adjusting for primary outcome of in-hospital mortality found improved survival in group who received hydroxychloroquine compared to standard of care (13.5% vs 26.4%, HR 0.34 (95% CI 0.25 to 0.45))
- secondary propensity matched analysis in a smaller proportion of patients demonstrated similar findings
- large observational study limited by its non-randomized nature; despite adjustment of primary outcome based on covariates, this does not address all known and unknown sources of confounding; conflicting evidence between this study and other non-randomized studies published to date

Mehra 2020-05-22

- ***this study has been formally retracted by the Lancet; the corresponding author of this large observational study has stated that the veracity of the database (i.e., Surgisphere Corporation) used to collection patient data could not be verified***

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 all 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 a New York quaternary care hospital 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

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

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

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

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

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.

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:
Oseltamivir is not recommended for treatment or prophylaxis of COVID-19.

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:
Interferon IV/SC is not recommended for the treatment of COVID-19. Ribavirin/Interferon (Inhaled) is not recommended outside of approved clinical trials.

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 multicentre 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 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 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 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 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.

(Hung 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, hazard 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.

(Xie 2020) reported a case of a 41-year old Chinese male who developed COVID-19 after attending an internal medicine-cardiovascular clinic in close contact with a patient with SARS-CoV-2. Patient developed ground glass opacity in both lungs, requiring admission to hospital. On Day 5 after admission, patient was SARS-CoV-2 oropharyngeal sample positive. Patient received lopinavir 400 mg/ritonavir 50 mg, arbidol 200 mg three times daily, and interferon-alpha-1b 50 ug inhaled twice daily for 7 days, and patient was discharged on Day 16 after full recovery. The authors comment on the removal of ribavirin from their treatment protocol due to no observed benefit when compared to lopinavir/ritonavir alone. They also comment on the common use of interferon for treatment of respiratory diseases in China with no strong supportive data.

(Davoudi-Monfared 2020) conducted an open-label randomized efficacy and safety trial in Iran evaluating interferon beta-1 alpha in severe COVID-19 treatment. Forty-two patients received interferon beta-1-alpha 44 mcg/mL SC three times weekly x 2 weeks and the national protocol (hydroxychloroquine plus Kaletra or atazanavir/ritonavir) vs. control national protocol (n=39 patients). Primary outcome was time to clinical response based on an ordinal scale. Mean age was 60 years. Time to clinical response did not differ (9.7 interferon beta-1 alpha vs. 8.3 days, p=0.95). For secondary endpoints, at Day 14, 67% interferon beta-1 alpha vs. 44% were discharged, and 28-day mortality was 19% interferon beta-1 alpha vs. 44%, p=0.015. This is a relatively small study, which shows potential benefit of interferon in combination with other treatments.

(Eslami et al, 2020) studied sofosbuvir and daclatasvir (antivirals against hepatitis C virus) vs. ribavirin 600 mg q12h and the national standard regimen (Kaletra and single-dose hydroxychloroquine) in severe COVID-19. Primary endpoint was start of medication until discharge from hospital with secondary endpoints of duration of ICU stay and mortality. Sixty-two subjects met inclusion, with 35 enrolled in sofosbuvir/daclatasvir arm vs. 27 in ribavirin arm. Median duration of stay was 5 days for sofosbuvir/daclatasvir group vs. 9 days for ribavirin group. Mortality in sofosbuvir/daclatasvir group was 2/35 (6%) vs. 9/27 (33%) for ribavirin. Further investigation in larger-scale trials is required.

(Kasgari et al, 2020) assessed efficacy of sofosbuvir and daclatasvir with ribavirin for treating COVID-19. Single-centre, randomized controlled trial in adults with moderate COVID-19 in Iran. Randomized to 400 mg sofosbuvir, 60 mg daclatasvir and 1200 mg ribavirin (intervention group) or to standard care (control group). Primary endpoint length of hospital stay. Forty-eight patients were recruited; 24 patients were randomly assigned to intervention group and 24 to control group.Median duration of hospital stay was 6 days in both groups (P = 0.398); number of ICU admissions in the sofosbuvir/daclatasvir/ribavirin group was not significantly lower than control (0 versus 4, P = 0.109). No difference in number of deaths between groups (0 versus 3, P = 0.234). Cumulative incidence of recovery was higher in the sofosbuvir/daclatasvir/ribavirin arm (Gray's P = 0.033). Larger randomized trials required.

(Rahmani et al, 2020) in open-label, randomized clinical trial in Iran, adult patients (≥18 years old) with severe COVID-19 were assigned (1:1) to IFN group or control. Patients received IFN β-1b (250 mcg subcutaneously every other day for two consecutive weeks) along with the national protocol medications vs. the control who received only national protocol medications (lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine for 7–10 days). Primary outcome was time to clinical improvement. Secondary outcomes were in-hospital complications and 28-day mortality. Eighty patients were enrolled and 33 patients in each group completed study. Time to clinical improvement in IFN group was significantly shorter than control group ([9(6–10) vs. 11(9–15) days respectively, p = 0.002, HR = 2.30; 95% CI: 1.33–3.39]). At day 14, percentage of discharged patients was 78.79% and 54.55% in the IFN and control groups respectively (OR = 3.09; 95% CI: 1.05–9.11, p = 0.03). ICU admission rate in

control group was significantly higher than IFN group (66.66% vs. 42.42%, p = 0.04). Duration of hospitalization and ICU stay were not significantly different between groups. All-cause 28-day mortality was 6.06% and 18.18% in IFN and control respectively (p = 0.12). IFN β-1b was effective in shortening time to clinical improvement without serious adverse events in patients with severe COVID-19; admission in ICU and need for invasive mechanical ventilation decreased. Further randomized clinical trials with large sample size are needed.

(Monk 2020) evaluated the safety and efficacy of nebulized interferon beta-1a (SNG001) for treatment of COVID-19 in R, DB, PC, phase 2 trial in adults (non-ventilated). Nebulized interferon (n=50) vs. placebo (n=51) x 14 days, plus standard of care with a 28-day follow-up. Primary outcome was change in clinical condition on WHO Ordinal Scale for Clinical Improvement (OSCI) during the dosing period (9-point scale: 0 - no infection; 8 - death). At baseline, 37 interferon vs. 29 placebo required supplemental oxygenation. Median time to initiation of treatment was 10 days. Interferon had greater odds of improvement on OSCI scale (odds ratio 2·32 [95% CI 1·07–5·04]; p=0·033); interferon more likely to recover to an OSCI score of 1 (no limitation of activities) (hazard ratio 2·19 [95% CI 1·03–4·69]; p=0·043). On Day 28, 58% interferon vs. 35% placebo recovered (OSCI 0 or 1). 3 interferon were intubated vs. 5 placebo; 3 deaths in the placebo group and none with interferon. Interferon was well tolerated; headache (7 [15%] patients interferon vs. 5 [10%] in placebo). Authors suggest potential for more rapid recovery. Limitations included validity of OSCI score and definition of change in clinical condition, which was primary endpoint, non-critically ill, and small sample size. Interferon may offer some benefit, but requires further study in larger trials.

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 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 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.

Ivermectin

Recommendation:
Ivermectin is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

In a systematic review and meta-analysis of RCTs (6 published, 4 non-peer-reviewed) by Roman et al published in *Clinical Infectious Diseases* (June 2021), the benefits and harms of ivermectin in COVID-19 patients were evaluated. Ten RCTs (1 in Spain and 9 in low- and middle-income countries) with sample sizes ranging from 24 to 398 patients were included (N=1173) [8 mild, 1 moderate, and 1 mild-moderate disease] with 5 to 30 days follow-up. Ivermectin did not reduce all-cause mortality (RR 0.37, 95% CI 0.12-1.13, I^2=16%, *very low quality of evidence* (QoE)), length of stay (mean difference 0.72 days, 95% CI -0.86-2.29, I^2=0%, *low* QoE), or adverse events (relative risk 0.95, 95%CI 0.85-1.07, I^2=0%, *low* QoE) in mild COVID-19 disease. Main limitations included high risk of bias in 8 RCTs, differences in comparator groups (placebo or standard of care), and *low* to *very low quality of evidence* to support the outcomes. Based on this well-designed study, ivermectin does not appear to be effective for treatment of COVID-19. Another systematic review and meta-analysis by Bryant et al was published in the *American Journal of Therapeutics* in June 2021. Twenty-four RCTs (N=3406) with 22 treatment and 3 prophylaxis trials (6 published, 18 non-peer-reviewed) ranging from 24 to 476 patients were included [16 mild-moderate, 6 severe disease]. Ivermectin appeared to reduce risk of death (2.3% vs. 7.8%, average risk ratio (aRR) 0.38, 95%CI 0.19-0.73, I^2=49%, *moderate-certainty evidence*, [N=2438-15 trials]) with no differences in severe adverse events (aRR 1.65, 85%CI 0.44-6.09, I^2=0%, *low certainty evidence*). For prophylaxis, ivermectin may reduce risk of infection but the studies were of low quality (5% vs. 29.6%, aRR 0.14, 85%CI 0.09.-0.21, *low certainty evidence*). Since the majority of studies were non-peer-reviewed trials with methodological variances and inadequate statistical significance, no definitive conclusions can be drawn.

Castaneda-Sabogal et al. assessed outcomes of ivermectin in ambulatory and hospitalized COVID-19 patients in a systematic review and meta-analysis. Published and pre-print randomized-controlled, non-randomized, and retrospective cohort trials were included. Primary outcome was overall mortality and secondary outcome was recovered patients. Twelve studies (5 retrospective cohort studies, 6 RCTs, and 1 case series met criteria (2 USA, 2 South Africa, 1 Iraq, 2 Spain, 1 Iran, 4 Bangladesh). Seven-thousand-four-hundred-and-twelve patients with a mean age of 47.5 yrs (SD 0.5) (58% male) were analyzed. Ivermectin was not associated with reduced mortality (logRR: 0.89 95%CI 0.09-1.70, p-0.04, I2 84.7%) and not associated with improved patient recovery (logRR 5.52, 95%CI – 24.36 to 35.4, p=0.51, I2 92.6%). Mortality was based on 5 retrospective studies (n=3607) and recovery on 3 pre-print retrospective studies (n=397). Overall, studies had low certainty of evidence based on study design, risk of bias, inconsistency, indirectness, and imprecision. The authors concluded that there was insufficient certainty and quality of evidence to recommend ivermectin to prevent or treat ambulatory or hospitalized patients with COVID-19. Limitations included: majority of studies were non-peer reviewed preprints (2 RCTs and 3 retrospective studies were published), level of evidence is low as retrospective and case series data were combined in the analysis, ambulatory (n=2) and hospitalized (n=5/8) patients

were combined, methodological designs varied between studies, ivermectin regimens were different in the studies, and most studies have high risk of bias and low certainty of evidence. Based on the limited published evidence and the methodological designs of the present studies, it is inconclusive whether ivermectin has any benefit in the prevention or treatment of COVID-19 at this time.

Ascorbic Acid and Vitamin D

Recommendation:
Ascorbic acid and Vitamin D are not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

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:
    - Thomas et al 2021: NCT04342728 COVIDAtoZ open label RCT in a single health system in the US (sites in Ohio and Florida) using ascorbic acid 8000 mg/day (in 2-3 divided doses), zinc gluconate 50 mg/day, ascorbic acid with zinc gluconate or standard of care x 10 days in 214 adult outpatients who test positive for COVID-19. Primary outcome: number of days to 50% reduction in cumulative 12 symptom score. Due to slow enrollment (projected enrollment of 520 patients), an interim analysis was done and the trial was stopped for futility (conditional power of <30% in all treatment arms). Mean baseline score for 4 symptom score: 4.3/12; baseline score for 12 symptom score: 11.6/36. No statistically significant difference in time to reduction in 50% of symptom score or in other secondary outcomes. 39.% of ascorbic acid only arm, 32.1% of ascorbic acid/zinc arm, 18.5% zinc only arm versus 0% of standard care arm experienced adverse effects due to supplementation (primarily nausea, diarrhea, stomach cramps).
    - Zhang J et al 2021: NCT04264533 Multi-centre, double-blinded, placebo-controlled trial in Wuhan, China using ascorbic acid 12g IV over ~4 hours q12h x 7 days versus bacteriostatic water in adults (18-80 yrs) within 48 hours of admission to ICU with severe/critical SARI (PF<300 mmHg) due to COVID-19. HC 1 mg/kg/d permitted if rapid deterioration of hypoxemia, ARDS or shock. Primary outcome: invasive mechanical ventilation free days in 28 days. Study terminated early (Mar 2, 2020) prior to reaching sample size of 140 due to low enrollment. n=56. Mean age 66.7, 66% male, APACHEII 13.5, mean duration of symptoms to enrollment was 17 days, 32.1% corticosteroid use. Primary outcome: 26 days with vitamin C vs 22 days with placebo, HR 4.8 95%CI -4.7-7.2,

p=0.58. 27 secondary outcomes, no adjustment for multiplicity. No treatment associated adverse events.

- Jamali Moghadam Siahkali J et al. 2021: Open label RCT of 60 adult patients admitted with PCR-confirmed or clinical suspicion of COVID-19 with O2 saturation of 93% or less randomized to receive vitamin C 1.5 g IV q6h x 5 days + standard care (lopinavir/ritonavir 400/100 mg bid and single dose of hydroxychloroquine 400 mg) vs standard care alone. Corticosteroids were provided only if clinical deterioration, as methylprednisolone 125 mg IV daily x 3 days. Primary outcomes of mortality, duration of hospitalization and ICU admission. No differences found in mortality, or ICU length of stay. Patients receiving vitamin C stayed in hospital for 8.5 days versus 6.5 days in standard care arm (p=0.028).
- Kamel A et al 2020: Case series of 22 adult patients admitted to a hospital in Saudi Arabia who received 3-5 days of quercetin 800 mg, bromelain 165 mg, zinc 50 mg, and ascorbic acid 1 g daily. No change in laboratory parameters following supplementation. No other clinical or safety outcomes reported, however, authors note the administration of these supplements is safe.
- Khan HMW et al 2020: Case report of a 74 year old female admitted for elective TKR, found to be SARS-CoV-2 positive. Started on hydroxychloroquine, azithromycin, ascorbic acid 1g PO bid, and PO zinc on day 4 of admission. Developed signs/symptoms of cytokine storm with elevated interleukin 6 levels on day 6, started on colchicine, and on day 7 of admission started on 11g of ascorbic acid given via intravenous continuous infusion. IV ascorbic acid and PO zinc were continued for 10 days total. Extubated on day 3 of IV ascorbic acid therapy. Authors attribute patient's rapid recovery to use of intravenous ascorbic acid.
- Hiedra R et al 2020: Case series of 17 patients identified sequentially with nasopharyngeal swab PCR positive for SARS-CoV2, requiring FiO2 of ≥30%, and received vitamin C 1 g IV q8h x 3 days. 59% African-American, mean age 64, vitamin C started at median 3 days of admission and median 8 days from symptom onset. 10/17 received methylprednisolone, 14/17 received hydroxychloroquine, and 5 patients received tocilizumab. D-dimer and ferritin were reduced after vitamin C therapy.
- 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.

Vitamin D plays a role in adaptive immunity and cellular differentiation, maturation and proliferation of various immune cells. Reduced vitamin D levels in calves has been suggested as a risk factor for bovine coronavirus infections.

In vitro: no data found specific to SARS CoV-2

Human data:

- Stroehlein JK et al 2021: Cochrane Systematic Living Review that included Murai et al, Rastogi et al and Entrenas Castillo et al. Authors conclude that there is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment of COVID-19.
- Murai IH et al 2021: Double blind, placebo controlled RCT in Brazil (n=240). Adult patients with COVID-19 and RR≥24, O2 saturation of ≤93% on room air, or risk factors for complications were randomized to receive vitamin D3 200000 IU PO once versus placebo. Primary outcome of time to hospital discharge (based on criteria: no supplemental O2 in last 48 hours, no fever in last 72 hours, O2 saturation >93% on room air without distress). No difference found in time to hospital discharge, mortality, admission to ICU, or mechanical ventilation requirement. Statistically significant increase in vitamin D levels found with treatment.
- Rastogi A et al 2020: Placebo controlled RCT in India (n=40). Adult patients with mild or asymptomatic COVID-19 and without comorbidities were admitted to hospital. Those with vitamin D deficiency (<20 ng/mL) were enrolled to be randomized to cholecalciferol 60000 IU daily x 7 days (up to 14 days, if repeat level at 7 days was <20 ng/mL), then 60000 IU qweekly vs placebo. Primary outcome: SARS CoV2 RNA negative before day 21. 62.5% of intervention arm vs 20.8% of placebo arm achieved RNA negativity at day 21.
- Munshi R et al: Meta-analysis of studies that reported vitamin D levels in patients with COVID-19. Studies also required to have at least one pair-wise comparison of severe vs non-severe outcome, ICU vs ward admission, live vs death. Seven studies with 1368 patients were included. Patients with poor prognosis (ARDS/mechanical ventilation, ICU admission or death) had significantly lower vitamin D levels (standardized difference -5.12 95%CI -9.14 - -1.10 p=0.012)
- Ohaegbulam KC et al 2020: Case series of 4 patients hospitalized at Long Island Jewish Forest Hills Hospital with PCR confirmed COVID19 given oral cholecalciferol at 1000 IU daily or ergocalciferol 50000 IU daily for 5 days. All patients were identified to be vitamin D deficient. The two patients who received high dose ergocalciferol appeared to recover more rapidly than those receiving standard dose cholecalciferol. Ergocalciferol and cholecalciferol are not bioequivalent.
- Entrenas Castillo M et al 2020: Parallel pilot, randomized open-label, double masked trial part of the Covidiol trial (NCT04366908) that included 76 consecutive hospitalized with COVID-19 (CXR with evidence of viral pneumonia and PCR positive for SARS CoV2) and CURB-65 score of >1. All patients received hydroxychloroquine, azithromycin and those with pneumonia and NEWS score ≥5 received ceftriaxone. Patients randomized to receive in a 2:1 fashion, calcifediol 0.532 mg or nothing on day 1, then 0.266 mg daily or nothing on day 3-7. Outcomes of interest were ICU admission, hospital discharge or death. Of the patients receiving calcifediol, 1/50 patients was admitted to ICU. 13/26 patients of the 'no-calcifediol' arm required ICU admission. Two patients died in the 'no-calcifediol' arm and none in the treatment arm. 61.54% (no-calcifediol) vs 48% (calcifediol) had at least 1 bad prognostic risk factor. The Covidiol trial is not yet recruiting.
- Tan CW et al 2020: Cohort study that included all consecutive patients with COVID-19 who were 50 years old or older admitted to a single centre in Singapore between January 15 and April 15, 2020. Patients admitted after April 6th who were more than 50 years of age, and not requiring oxygen or ICU support, received oral vitamin D3 1000 IU daily, magnesium oxide 150 mg daily,

and vitamin B12 500 mcg daily for up to 14 days (n=17). Any patient during the study period that was more than 50 years of age was in the control group (n=26). Primary outcome was requirement of oxygen therapy if oxygen saturation was below 95% and/or requirement of ICU support (not defined). Intervention arm was younger, had less comorbidities, and more likely to have a normal CXR on admission. More patients in the control arm received therapies such as remdesivir. 17.6% in the intervention arm vs 61.5% in the control arm reached the outcome. Limitations include small study size and non-randomized design.

- NCT04334005 Randomized, double blind controlled trial in Granada Spain using vitamin D 25000 IU comparing to standard care (NSAIDs, ACEi, ARB, or thiazolidinediones, based on current recommendations) in adults 40-70 years of age with non-severe symptoms of respiratory infections. Primary outcome of all-cause mortality. Not yet recruiting.
- NCT04363840 LEAD COVID-19 open-label RCT in New Orleans using no intervention vs aspirin 81mg PO daily vs aspirin 81 mg PO daily with vitamin D 50000 units PO weekly (in those who are vitamin D deficient) x 2 weeks. Primary outcome of hospitalization at 2 weeks.
- NCT04385940 Blinded RCT in Alberta using high (ergocalciferol 1.25 mg) vs low dose vitamin D (vitamin D3 1000 IU) in adults with COVID-19. Primary outcome of number of participants with symptom recovery. Study estimated to be completed by December 2020.
- NCT04344041 CoVit trial - multicentre, open label RCT in France using single high-dose vitamin D 400000 IU vs 50000 IU orally in patients 70 years of age and older with PCR confirmed COVID-19 OR CT chest findings suggesting a viral pneumonia. Primary outcome of death at 14 days. Study estimated to be completed in May 2021
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Convalescent Plasma

Recommendation:
Convalescent plasma[#] is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

Convalescent plasma for treatment of COVID-19 has been explored through numerous well-designed RCTs, all of which have been negative. We support any further efforts of 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. The use of CP as a treatment for COVID-19 was approved by the US Food and Drug Administration on March 25, 2020 as an emergency investigational new drug, and on September 23 issued an update stating that CP 'may be effective'. The IDSA Guidelines recommend limiting the use of convalescent plasma in the context of a clinical trial. In Canada, CP therapy for COVID-19 is currently available only as an investigational drug treatment for participants in the CONCOR-1 clinical trial. The CONCOR-1 clinical trial is currently underway and involves more than 50 hospitals across Canada with the intention to recruit 1,500 participants; however due to the lack of donors Island Health does not currently have any study sites. A unit of CP is estimated to be approximately $700-1000 CND.

To date, there have been numerous published RCTs that have failed to show a benefit of CP in hospitalized patients with COVID-19. Despite this, one positive trial was recently published that documents a small benefit of CP if given to outpatients with mild illness, which suggests that convalescent plasma may play a protective rather than a therapeutic role in COVID-19. However, due to lack of availability of CP as well as logistical challenges with administration, CP remains available through clinical trials only. Questions also remain about the antibody titer that should be used when treating patients with COVID-19, and if timing of administration is an important consideration. The summary of these trials is found below, and is adopted from a comprehensive literature review available on the IDSA website.

Guidelines

IDSA guidelines recommend against COVID-19 convalescent plasma among patients hospitalized with COVID-19 (conditional recommendation, low certainty of evidence). Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. NIH guidelines state that "data are insufficient to recommend for or against" the use of convalescent plasma.

Human Data

The largest support for the use of convalescent plasma to date comes from a large uncontrolled observational cohort study of 35,000 US patients who received CP treatment as part of the Expanded Access Program (EAP) that has led to its wide-spread use.

EAP COVID-19 Plasma Consortium:

- 35,322 patients 18 years or older with laboratory-confirmed COVID-19 who received at least one dose of convalescent plasma were observed as part of the EAP led by the Mayo Clinic and the National Institute of Health
- All eligible patients under this program from April 4, 2020 to July 4, 2020 were included in the analysis. There was no placebo, but different groups of patients were compared to each other on the basis of:
    - The month they received the CP (patients early on in the program tended to receive CP later in the disease)
    - Antibody titers achieved post-transfusion
    - 7- and 30-day mortality was assessed and comparisons were made between groups on the basis of timing of the CP (3 days or fewer vs. over 3 days) and IgG titers
- 52.3% of patients were critically ill in the ICU at the time of plasma transfusion; patients needed to be "severely ill" or at "high risk of progression" by the treating team to be considered for CV.
- Patients received one 200ml unit of CV with additional doses permitted if they were justified
- The study reported that 7-day mortality rate was 8.7% [95% CI 8.3%-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis ($p<0.001$). Similar findings were observed in 30-day mortality (21.6% vs. 26.7%, $p<0.0001$).
- The study also reported a trend towards lower mortality on the basis of plasma IgG concentrations. (8.9% vs. 11.6% vs. 13.7% for those receiving high, medium or low IgG plasma), $p<0.048$.

The results of this yet to be published study are difficult to apply due to the uncontrolled nature of the design. While the mortality benefit in those who got CP earlier and received more IgG containing products is promising, this result is prone to innumerable sources of confounding. One is the trend of faster administration of CP as the pandemic progressed, which could have been due simply to a better understanding of the disease and lower admission rates later in the study period. While adjustments were made for different covariates such as age, gender, receipt of remdesivir or steroids, the number of covariates possible makes this analysis difficult to justify. It is also impossible to determine how CP impacts mortality when compared to no treatment, as opposed to simply being compared to a different product and timing of administration. As such, we agree with the study authors that the results of the EAP can be used as an exploratory analysis but not as definitive support for the use of CP.

Besides one positive observational trial in outpatients, there have been several negative RCTs, two case reports, a retrospective case series (n=5), and a prospective cohort study (n=20) that have evaluated CP for the treatment of COVID-19. Results from these studies on mortality are mixed with the RCTs in inpatients showing no benefit. While viral clearance appears to be faster, CP does not appear to have any effect on duration of illness or hospital length of stay.

Horby et al (March 2021; preprint): Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial
Study Design: A randomized, controlled open-label platform trial of convalescent plasma versus usual care in 11,558 hospitalized U.K. COVID-19 patients

Patient population:

- Hospitalized U.K. patients of any age with confirmed or suspected SARS-CoV2 infection.
- Mean age was 63.5 years; 87% were receiving oxygen only and 5% were receiving mechanical ventilation. Most were receiving steroids.
- Of 9,385 patients with available baseline SARS-CoV-2 antibody, 62% were seropositive. Median time from symptom onset to randomization was 9 days.
- Patients received plasma donations with sample: cutoff ratio of ≥6 (EUROIMMUN IgG ELISA vs. spike glycoprotein), which correlates with a neutralizing antibody titer of >1:100 (U.S. FDA considers EUROIMMUN sample: cutoff values of >3.5 to be high-titer).
- There was no placebo - patients in the comparator arm were randomized to standard of care.

Primary endpoint: All-cause mortality at 28 days and 6 months.

Key findings:

- No difference between participants who received plasma and those who received placebo with respect to mortality (24% vs. 24%; RR, 1.00; 95% CI, 0.93 to 1.07; p=0.93).
- An exploratory post hoc analysis of primary outcome comparing participants randomized before and after Dec. 1, 2020 (which is when the B.1.1.7 variant emerged in the U.K.) showed similar results.
- The 38% of participants who were seronegative at baseline had a markedly higher 28-day mortality than seropositive participants, but this group did not benefit from convalescent plasma.
- In January 2021, the data monitoring committee recommended that further recruitment would not provide convincing evidence of mortality benefit in any subgroup and that the study stop.

Limitations:

- It is not clear whether there would have been benefit had participants been transfused earlier in course of illness.
- Fewer patients in the convalescent plasma group received IL-6 inhibitors than in the standard of care group (8% vs. 10%).
- The impact of corticosteroids on the immune response to convalescent plasma is unknown, but if it hampers response then it could explain the negative result, as 92% of the participants were on corticosteroids.

Simonovich et al. (February 2021) - A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

Study Design: PlasmAr, a randomized, controlled trial of convalescent plasma versus placebo in 333 hospitalized COVID-19 patients evaluating mortality or clinical status at day 30 after transfusion between those treated with convalescent plasma and placebo.

Patient population:

- Hospitalized adults with severe COVID-19 pneumonia (SARS-CoV-2 PCR positive, O2 sats <93% on room air, PaO2:FiO2 <300 mm Hg or SOFA score 2 or more points above baseline).
- Of the 215 patients who had a baseline anti-SARS-CoV-2 antibody, median titer was 1:50 (IQR, 0 to 1:800); 46.0% of patients had no detectable antibody level. Median time from onset of symptoms to study entry was 8 days (IQR, 5 to 10).
- Median anti-SARS-CoV2 Ab titer infused 1:3200 (IQR, 1:800 to 1:300); the minimum donor titer was set at 1:400 (either single or pooled units given), measured using the COVIDAR Argentina Consortium ELISA test.

Primary endpoint: Clinical status at day 30 on a 6-point ordinal scale.

Key findings:

- There was no difference between participants who received plasma and those who received placebo with respect to clinical status (OR, 0.83; 95% CI, 0.52 to 1.35; p=0.46).
- There was no difference between participants who received plasma and those who received placebo with respect to mortality (10.96% in convalescent plasma group vs. 11.43% in placebo group; RD, –0.46 percentage points; 95% CI, –7.8 to 6.8).

Limitations:

- It is not clear whether there would have been benefit had participants been transfused earlier in course of illness or had transfusions been given to those with milder disease.
- It is not clear how COVIDAR titer assay correlates to Ortho assay.
- Analysis of the neutralizing antibody titers was only available for 56% of the units.
- Prespecified subgroups (including those who received transfusion within 3 days) were all quite small, and thus likely underpowered to show differences.

O'Donnell et al. A randomized, double-blind, controlled trial of convalescent plasma in adults with severe COVID-19

Study Design: A small randomized controlled trial in NYC and Brazil looking at the impact of convalescent plasma versus control plasma on clinical status at 28 days.

Patient population:

- Adults hospitalized with SARS-CoV-2 PCR positive, infiltrates on imaging, room air oxygen saturation <94%.
- Excluded patients with duration of mechanical ventilation or ECMO of >5 days at screening. Duration of symptoms prior to randomization: 9 days.
- 81% of participants received corticosteroids; 6% received remdesivir (all in NYC); even distribution across groups.

- Neutralizing Ab titers available for 89% of convalescent plasma units (median titer 1:160; IQR, 1:80 to 1:320).
- Convalescent plasma for all study sites (including those in Brazil) was collected in NYC.
- Genomic sequencing on NP swabs was performed on a subset of Brazilian participants and found no evidence of neutralization-escape variants.

Primary endpoint: Clinical status at 28 days from randomization (WHO 7-point ordinal scale); changed from time-to-clinical-improvement out of concern that patients could worsen again after initial improvement.

Key findings:

- No significant difference in clinical status at day 28 was seen between groups.
- Significantly lower mortality was seen in the convalescent plasma group than in the group that received control plasma (12.4% vs. 24.6%, respectively; aOR, 0.47; p=0.068).
- Non-significant trends toward clinical improvement were seen when convalescent plasma was transfused within 7 days of symptom onset and when high-titer units were given.
- Post hoc analyses performed by country of site and found no difference in outcome.

Limitations:

- The trial was not powered to detect a mortality difference.
- The use of control plasma (while important for blinding) might have contributed to volume overload/thrombosis or in some way worsened outcomes.
- Titers in some transfused units were low.
- Convalescent plasma was given fairly late in progression of disease (9 days after symptom onset).

Libster et. al. 2021: Early High-Titer Plasma Therapy to Prevent Severe COVID-19 in Older Adults

Patient population:

- Randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers (over 1:1000) in older adult patients within 72 hours after the onset of mild COVID-19 symptoms conducted between June 4, 2020, and October 25, 2020, at clinical sites and geriatric units in Argentina.
- 80 patients received convalescent plasma and 80 patients received placebo. Patients who were > 75 years old (irrespective of current coexisting conditions) or between 65 and 74 years of age (with at least one coexisting condition, for example diabetes or hypertension) were included.
- Groups were well balanced; 62% were women and the mean age was 77.2 years.
- The primary endpoint was progression of disease to severe, which was defined as a respiratory rate > 30 breaths/min, an O2 saturation of <93% on room air or both.
- Patients were recruited through call centers similar to the BC COVID-19 telephone line and were called to ask to participate in the trial if they appeared to meet the inclusion criteria and tested positive for COVID-19. If they agreed to participate, they were transported to an infusion facility by ambulance. Over 1/3 of patients refused to participate and leave their homes. Follow-up was conducted by home visits by health care professionals.

- Donor plasma was obtained by calling patients who tested positive for COVID-19 at least 30 days prior. Phlebotomists performed home visits to screen patients' plasma to ensure a high titer. Only 21% of donors had high-titre plasma.
- Severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and in 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P=0.03).
- The relative risk reduction with convalescent plasma was 48%, and the number needed to treat to avert an episode of severe respiratory disease was 7 (95% CI, 4 to 50).
- Secondary endpoints favoured CP but did not reach statistical significance. Four convalescent plasma recipients (5%) and 10 placebo recipients (12%) had life-threatening respiratory disease, and 5 (6%) and 6 (8%), respectively, had a critical systemic illness. Two vs. 4 patients died.
- The trial was stopped early due to difficulties in recruitment driven by the decreasing number of cases in Argentina.
- Due to the study procedures, the external generalizability of this trial has been called into question. Replicating the trial would need to involve call centres, ambulance services, administration facilities and health care providers able to conduct home visits.
- High reluctance to enroll in the study was also seen; nearly ⅓ of eligible elderly patients, even if capable of actively participating in their care, refused to consent.
- The external generalizability to BC patents is also reduced as the study found enrollment difficult once the test positivity rate dropped to below 50%; it is less than 10% in BC currently.
- Finally, lack of convalescent plasma, particularly the high-titre type which is available from only ~20% of COVID survivors, and overall low donor pool would make operationalization of such an intervention nearly impossible.

Li et al. 2020: A randomized unblinded controlled trial of hospitalized patients at 8 Chinese hospitals

- 103 patients with a positive COVID-19 PCR exhibiting severe (requiring O_2) or life-threatening (requiring ICU admission) symptoms were randomized to CP (N=52) and control (N=51).
- There was no significant difference in baseline characteristics and illness factors between groups but many patients received antivirals, herbal medicines and other unproven therapies
- CP was given at a mean volume of 200ml with a Ig-G titer of 1:1280
- The primary outcome was time to clinical improvement within 28 days, defined as either discharge from hospital or a 2-point improvement on a 6-point clinical scale; secondary outcomes were mortality, time to discharge and viral clearance
- There was no significant difference in mortality for all patients (CP=15.7% vs control=24%) irrespective of disease severity; there was also no difference in overall rates of clinical improvement or length of stay
- Patients who were severely ill (but not those with life-threatening disease) had a shorter time to clinical improvement (13 vs. 19 days; p=0.03). There were also higher rates of viral clearance at various time points (e.g. 87.2% for the CP group at 72 hours vs. 37.5% for control)
- The study attempted to recruit 200 patients but could not due to diminishing cases which likely lead to inadequate power to detect a difference in outcomes

Zeng et al 2020: A case series of 21 patients from two Chinese hospitals of whom 6 received CP therapy and 15 were used as controls

- All patients had severe COVID-19 and were admitted to the ICU

- Mean volume of CP given was 300ml; the volume given was not standardized or specified. Some patients received multiple doses for unknown reasons
- Outcomes were mortality, hospital discharge, ADRs and viral clearance
- The study reported no difference in mortality between groups (83.3% vs. 93.3%). The extremely high mortality raises questions to the generalizability of the results
- There are various methodological issues with this study leading to poor quality, including observational nature, small sample sizes, lack of power calculations, lack of adjustment for confounders and no standardized CP dosing

Shen 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 2020 followed the Shen 2020 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 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.

Overall, convalescent plasma initially posed a potential treatment option, however thorough investigations for the treatment of COVID-19 has thus far failed to show its superiority over placebo or standard of care.. The Canadian Blood Services has completed enrollment in their CONCUR trail, and the medical community is awaiting results from this large Canadian study.

Intravenous Immunoglobulin G (IVIG)

Recommendation:
Intravenous immunoglobulin G (IVIG) is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

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 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 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.

Monoclonal Antibodies and Antibody Cocktails

Recommendation:

CRITICALLY ILL:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) are NOT recommended. An RCT of REGN-COV2 in this population was halted due to signals of harm. Regdanvimab conditions for use state that it may be associated with worse outcomes in the critically ill. RECOVERY showed no benefit in the subgroup that required organ support. Various guidelines (IDSA, NIH, INESSS) recommend against mAbs in this setting.

SEVERELY ILL:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) are not recommended. MAbs have shown inconsistent results in RCTs. TICO was stopped for futility as mortality was numerically higher in the Bamlanivimab arm. RECOVERY demonstrated a mortality benefit with REGN-COV2, but only in seronegative patients, with signals of harm in seropositive patients. Reliable rapid antibody tests to identify the target population are not readily available and all mAbs remain unapproved in Canada for in-patients with COVID-19.

MILDLY ILL:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) IV have shown to reduce hospitalization rates (although not mortality or length of stay) in UNVACCINATED outpatients at high-risk of complications due to comorbidities (age >40 with a comorbidity like obesity or hypertension). Due to high vaccination rates and barriers to operationalizing outpatient IV administration outside of clinical trials, the clinical application of these studies is limited. **mAbs may be considered on a case-by-case basis in those inadequately immunized (unimmunized, partially immunized or inadequate immune response) with mild disease AND who are at high risk of developing severe COVID-19-related complications.** The subcutaneous route has shown similar reductions in viral loads, but clinical data is lacking and would still present operational barriers such as multiple injections and required observation time.

PROPHYLAXIS:

Bamlanivimab/etesevimab IV has shown to reduce the development of symptomatic COVID-19 as prophylaxis in unvaccinated LTC residents, as has subcutaneous REGN-COV2 given to unvaccinated, seronegative, PCR-negative household contacts if given within 96 hours of exposure. Due to lack of reliable rapid tests to identify the target population within the prophylaxis window, lack of impact on hospitalization rates or mortality and low generalizability of these studies, **mAb administration is not recommended for post-exposure prophylaxis**.

Bamlanivimab

Bamlanivimab (initially called Ly-CoV555) is a monoclonal antibody against the Sars-CoV-2 spike protein that blocks viral entry and subsequent replication. The investigational lab has received attention after the publication of the Phase 2 trial (Blaze-1) that evaluated its impact on viral load and selected clinical endpoints. Since then, the drug has been controversial due to updated negative phase 2/3 results and the emergence of variants both escaping the drug leading to mutations, and general resistance to it as monotherapy. Recently, the US has revoked the EUA for bamlanivimab monotherapy and Health Canada issued a warning cautioning clinicians regarding its use.

Chen et al 28-10-2020: SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Of note, while the data from BLAZE-1 were first published by Chen et al in NEJM, the final analysis was re-published in JAMA. The results, however, differ and the differences are delineated below under Gottlieb et al.

- A phase 2 randomized double-blind placebo-controlled trial of 452 outpatients diagnosed with mild to moderate Covid-19.
- Mild-moderate disease was defined as symptoms of Covid-19, including cough, fever, malaise and shortness of breath, but not requiring oxygen support or hospitalization.
- Patients were diagnosed by an NP swab and randomized and treated at an outpatient clinic within 72 hours of a positive Covid-19 test.
- Patients were randomized into 4 groups: bamlanivimab 700mg (initial optimal dose determined after a Phase 1 trial, N=101 patients), 2800mg (N=107 patients), 7000mg (N=101 patients) and placebo (N=150 patients).
- The primary endpoint was reduction in viral load, determined using RT-PCR performed on specimen from NP swabs, at a pre-specified analysis time point of day 11 after receiving the study drug.
- Secondary outcomes included safety data, symptom scores using an 8 question questionnaire and a composite endpoint of hospitalization, emergency room visit and death.
- Analysis of data was based on an intention to treat. No adjustments were made for multiplicity.
- While 69% of patients had other risk factors that could increase their risk for developing severe Covid-19 (e.g. obesity, one co-existing illness), the majority of patients were young (average age 45 years) and with mild illness only (79%).
- Primary outcome: by day 11, all patients, including those receiving placebo, had a log viral load reduction by -3.81, which corresponded to a 99.9% elimination of the viral load.
- Pooled analysis of all three doses of bamlanivimab was not statistically significantly different from baseline. Only the 2800mg dose had a statistically significant impact on viral load over placebo (-0.53, CI -0.98 to 0.08), where the 700mg and 7000mg doses did not.
- Secondary outcomes of hospitalization/emergency room visits at day 29 were reported to be lower in those who received bamlanivimab (5 of 309 patients vs. 9 of 143 patients, 1.6% vs. 6.3%), however no statistical analysis was reported on this outcome. It is impossible to determine whether this difference is statistically significant as the pre-planned logistic regression was not performed and cannot be done through critical appraisal using only the aggregate data reported. It is unclear whether this outcome was driven by emergency room visits, hospitalizations or both.
- Symptom scores were taken daily for 11 days, and were not statistically significant at most time points with the exception of day 4. Most patients had only mild illness.

- Safety endpoints were explored and overall no serious ADRs were reported, however patients in the bamlanivimab group had a higher rate of allergic and infusion reactions than placebo (2.3% vs. 1.4%). The manuscript noted that no infusions had to be discontinued, however in the nomogram submitted to Health Canada for review, it was noted that in the Phase 1 trial there were 2 serious infusion reactions (1 anaphylaxis and 1 other serious reaction) that required significant intervention. For this reason, the Blaze-1's protocol required a 2 hours post infusion observation period with treatment on stand-by.

The trial's results, while potentially hypothesis generating, cannot be used to guide clinical decisions regarding the role of this drug, and further study is required. A reduction in viral load is insufficient evidence to warrant the use of bamlanivimab, particularly since it was not observed in all treatment groups, and not statistically significant overall. While the lower hospitalization rates are promising, as a secondary outcome with no statistical analysis, it too is hypothesis generating at this time. Blaze-2, a trial looking at the efficacy of bamlanivimab in preventing Covid-19 in patients exposed to Covid-19 in long term care facilities is currently enrolling, and may be better suited to define a niche for its use.

Significant pragmatic concerns have also been brought forward by the medical community regarding the operationalization of administering bamlanivimab as per the trial's protocol. Patients who recently test positive for Covid-19 need to be admitted to medical daycares or facilities able to administer IV medications, posing a significant risk by increasing health care exposure to the virus. Three hour infusions and short stability at room temperature, combined with a significant observation and monitoring period put additional strain on health care workers and resources. Furthermore, the safety of the drug in light of serious reactions observed in the Phase-1 trial has been brought to question, and requires additional evaluation.

On the basis of the above mentioned publication, bamlanivimab monotherapy obtained emergency use authorization in the US, and a similar approval order in Canada. However, the evidence for bamlanivimab has evolved over the last several months, particularly due to the emergence of variants resistant to the MAB. Furthermore, the final analysis of BLAZE-1 was published in JAMA, which refutes that bamlanivimab monotherapy is useful for the treatment of COVID-19, having failed to demonstrate any benefit on surrogate and clinical endpoints. Due to this, the bamlanivimab procured by Health Canada has been largely unused.

Gottlieb et al. JAMA. 2021;325(7):632–644 - Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19

- Recognizing that new variants such as P1, B135, California and NY variants are resistant to bamlanivimab monotherapy, the cocktail (bamlanivimab 2800mg- etesevimab) was added as the fifth study arm to the BLAZE-1 trial.
- This publication represents a "final analysis" of this trial but includes the results of the dual therapy arm.
- The combination therapy of bamlanivimab 2800mg/etesevimab was administered after the previous 4 – arm analysis was conducted, and occured after August 2020.
- Most of the controls for this arm were historical, having been enrolled from the first part of the study, and not randomized to placebo at the same time. The trial only added 13 additional controls during the combination therapy arm after August 2020

- The primary outcome was again viral load; the 2800mg dose of monotherapy no longer met statistical significance as it did in the preliminary review
- No monotherapy arm (700mg, 2800mg or 7000mg) was statistically significantly better than placebo in reducing hospitalizations or any other endpoint.
- This time, the combination therapy was SS better than placebo in reducing viral load, although the clinical significance of this result is unclear as all patients had a very large reduction in viral load over time.
- For secondary outcomes, there were approximately 80 comparisons performed; some were statistically significant favoring the combination therapy with etesevimab. For example, the combination therapy appeared to be better at reducing hospitalization than the historical placebo group (9 events vs. 1 event).
- However, because these were non-contemporaneous controls, represented an exploratory outcome and no statistical adjustment for multiplicity, the results were not given much weight. They represent more of a hypothesis testing cohort study as opposed to a rigorously conducted RCT that informs our recommendations.

Since then, several press releases have stated that BLAZE-1 has added yet another cohort arm, this time a lower bamlanivimab dose (700mg) with etesevimab. Again, this is a dose finding exercise, which represents more of a Phase II study as patients were not randomized to placebo, but rather compared to historical controls collected in the earlier part of BLAZE-1 above. This part of the study has not been published and as such recommendations regarding this treatment based on the press release cannot be made.

Another press release in January 2021 cited positive results from a study of exposed patients in LTC (BLAZE-2), stating that a 4200mg bamlanivimab dose reduced symptomatic COVID "by 80%" (no raw data given). The press release stated that the drug was actually also given to staff as many residents had challenges participating. The peer-reviewed publication of this trial was published in June 2021 by Cohen et al.

Cohen et al. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities - A Randomized Clinical Trial

Study Design: A randomized, double blind, placebo controlled clinical trial in 74 nursing facilities in the US designed to investigate the impact of bamlanivimab on the development of symptomatic COVID-19 if an outbreak was declared at the facility.

Participants:

- A total of 1175 participants enrolled in the study from August 2 to November 20, 2020. Database lock was triggered on January 13, 2021, when all participants reached study day 57.
- The study initially intended to enroll nursing home residents, however enrollment was challenged by lack of IV access, competing goals of care, and inability to provide informed consent. The enrollment was expanded to also include staff of the facilities.
- Within 7 days of detection of an index COVID case, participants were offered entry into the trial; COVID testing and serology were performed before randomization.
- Patients were randomized to bamlanivimab 4200mg IV as a single infusion or IV saline placebo

- Patients had to be at least 18 years of age, be asymptomatic and have presumably no COVID history, however study drugs were given before PCR results were available. Those who turned out to be positive for COVID (N=132) were not analyzed for the primary endpoint.
- Baseline characteristics varied between staff (N=666) and residents (N=300). Average age of residents was 76 vs. 53 years old in the overall population. 74% of participants were female. 41% of staff in the prevention group were considered high risk (at least one comorbidity associated with poor outcomes)
- Statistical analysis was performed using logistic regression and stratified by age and LTC facility.

Endpoints: The primary outcome was incidence of COVID-19, defined as the detection of SARS-CoV-2 by PCR and mild or worse disease severity within 8 weeks of randomization. Key secondary outcomes included incidence of moderate or worse COVID-19 severity and incidence of SARS-CoV-2 infection regardless of symptoms over the 57 day follow-up period.

Results:

- Overall, 11.9% (N=114 participants experienced mild or worse COVID) over the study follow-up period.
- Participants who received bamlanivimab had significantly reduced incidence of mild or worse COVID-19 compared with participants who received placebo (8.5% vs 15.2%; odds ratio, 0.43; 95% CI, 0.28-0.68; P < .001), with an absolute risk difference of −6.6% (95% CI, −10.7 to −2.6) and an NNT of 15.
- In the resident prevention population, incidence of mild or worse COVID-19 was significantly lower in the bamlanivimab group compared with the placebo group (8.8% vs 22.5%; odds ratio, 0.20; 95% CI, 0.08-0.49; P < .001), for an absolute risk difference of −13.7% (95% CI, −21.9 to −5.4).
- Among the staff in the prevention population, incidence of mild or worse COVID-19 was not significantly different in the bamlanivimab group compared with the placebo group (8.4% vs 12.2%; odds ratio, 0.58; 95% CI, 0.33-1.02; P = .06). However, if the high risk population was analyzed (high risk staff + residents), the difference was SS.
- Mortality was low (5 residents) and thus NSS.
- Adverse effects were infrequent and NSS. 3 participants in the bamlanivimab group experienced hypersensitivity reactions (0.5%).

Limitations:

- The study has various significant limitations that greatly reduce its external generalizability.
- First, the study was conducted before mass vaccination efforts were underway. It is unclear whether bamlanivimab would offer a significant benefit at the described effect size in a vaccinated population, or confer protection that is clinically meaningful.
- Further, bamlanivimab is not effective in neutralizing variants of concern (VOC) including P1 and 135 variants which were infrequently isolated during the study period. In March, the FDA revoked the Emergency Use Authorization for bamlanivimab due to these concerns, although the combination with etesevimab retains efficacy against these strains and remains available under the EUA. Therefore, the use of bamlanivimab monotherapy considering current VOC epidemiology is no longer advisable.
- Lastly, administering IV infusions in nursing homes proved to be operationally challenging. 74 nursing homes with outbreaks were required to enroll 300 resident participants. Many nursing

homes in BC have a nurse to resident ratio of less than 1:100; as such staffing available for administration of IV infusions outside clinical trials poses a major pragmatic barrier. Even with sufficiently trained staff within this RCT, the majority of eligible participants declined enrollment, could not establish an IV or had already contacted COVID. This was overcome in the trial by enrolling mainly staff; however the primary endpoint in staff did not reach statistical significance.

Bamlanivimab has also been evaluated in inpatients hospitalized with COVID. The results of this trial were negative and the study was halted early:

N Engl J Med 2021; 384:905-914 - A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19

- 314 patients were randomized to bamlanivimab vs. placebo; all patients received steroids and/or remdesivir if eligible. The primary end-point was sustained recovery at 90 days.
- Most patients at baseline were either not receiving oxygen, or were on less than 4 L; no one was receiving invasive ventilation but 15% were on Optiflow.
- There was no difference in sustained recovery between bamlanivimab and placebo (82% vs 79%), favourable pulmonary score at day 5 (50 vs 54%) or death (6 vs 3%). Of note, death was numerically doubled in the bamlanivimab arm (NS).
- The study was stopped early for futility.

Real world non-randomized cohorts evaluating monoclonal antibody therapy:

- At the end of March, 2021, a preprint of a large retrospective study from Utah was published on medrxiv, where outpatients with COVID participated in the EUA program of bamlanivimab in that state. https://www.medrxiv.org/content/10.1101/2021.03.15.21253646v1.full.pdf
- As the drug was scarce, some eligible COVID-positive high risk outpatients received it (N=594) while most did not (N=5536); those groups were compared retrospectively.
- Controls were also taken from before the program was implemented (N=7404). The drug was only given to those in the highest 10% of risk (average age 65 y/o plus co-morbidities) and propensity score weighted analysis was conducted to compare the three groups.
- The primary outcome of ED visits + hospitalization occurred in 75 (12.6%) MAB recipients, 1018 (18.4%) contemporaneous controls, and 1525 (20.6%) patients in the pre-implementation cohort, which was statistically significant when compared to either control group.
- Of note, 2/3 of the events were NOT hospitalizations but rather ED visits that did not lead to hospital admission.
- As a retrospective study, there are very large biases in who received the MAB and who did not when called or selected to do so. This bias is often referred to as “walking well” or survival bias.
- Patients could receive the infusion within up to 10 days testing positive, whereas controls presented to hospital, on average on day 4. Therefore, many of those who were sicker were hospitalized before they had an opportunity to receive the MAB.
- There were also nearly no variants circulating in Utah at the time of the study (late 2020).
- Therefore, the generalizability of the study is very low, and the methodology poses significant limitations.

Another real-world cohort was published in March 2021 on the pre-print website Rxiv by Rainwater at al: https://www.medrxiv.org/content/10.1101/2021.04.08.21254705v1

- Retrospective cohort of 598 patients at a single centre in the US who were eligible for bamlanivimab therapy when it became available in January 2021.
- The study attempted to capture bamlanivimab therapy administered to a racially diverse population.
- 270 patients received MAB therapy between January 1-15, 2021. Patients had to have tested positive on or before Dec 20, and presented for infusion therapy within 10 days of symptom onset; the remaining 328 served as historical controls.
- Some significant imbalances existed between treated and untreated patients; those untreated had significantly higher rates of hypertension, heart disease and obesity, while being on average three years younger. This again highlights the "walking well" bias.
- Statistical methods used included t-test and Chi-squared test and did not adjust for imbalances between the variables.
- It is unclear why patients used as controls were eligible for treatment but did not receive it.
- In the 30 days following a positive SARS-CoV-2 test result, five of 270 treated patients (1.9%) presented to the ED or required hospitalization within 30 days of a positive SARS-CoV-2 test result, compared to 39 of the 328 untreated patients (12%) ($p<0.01$)
- The results were not broken down between hospitalizations and ED visits; it is unclear what proportion of the admissions were actual hospitalizations.
- Those who did not receive treatment were, on average, admitted 4 days after COVID positive test, which could have prevented them from presenting for MAB therapy, which could have been given up to day 10. Survival bias was therefore high in the study.
- Due to significant other biases, for example that those with less comorbidities are more able to avail themselves of treatment, as well as the lack of statistical methods to adjust for them, the study has low external validity.

A case-control study in Clinical Infectious Diseases has also been published describing real-world use of EUA approved bamlanivimab in Michigan; however it shares the methodological issues of the above mentioned studies, plus additional flaws:

- This was a retrospective case-control study of outpatients diagnosed with COVID -19 between November 11, 2020 and January 19, 2021 in 10 hospital centers and associated clinics in the Chicago area.
- Patients were referred to receive bamlanivimab if they did not require hospitalization or oxygen therapy; those who received it were compared to those referred but who did not receive the drug.
- Exclusion criteria included testing positive before Nov 11, or symptoms of COVID lasting 15 days or more. Patients were included if they had symptom onset within 10 days and had tested positive no more than 5 days before the infusion appointment. Patients with certain risk factors were initially prioritized (e.g. age over 65, comorbidities), but the priority system was not utilized due to sufficient drug being available.
- Patients who were in the control group were therefore only placed in that group on the basis of cancelling the appointment/no show.
- A regression analysis was used for statistical analysis of the association of the receipt of bamlanivimab with the primary outcome of hospitalization within 30-days of positive COVID PCR, along with other variables associated with hospitalization.
- During the study period, 218 patients received bamlanivimab, and 185 did not; reasons for cancellation/no show were not documented in most patients but some (12.3%) declined therapy and some (4.3%) presented to the appointment with severe symptoms.

- There were a variety of imbalances between groups. Those receiving bamlanivimab were more likely to be white, English speaking and older. Patients who showed up for appointments were also more likely to be asymptomatic.
- Most patients that did not show up for the appointment were referred from the ED as opposed to from the ambulatory care clinics.
- The 30-day hospitalization rate was 7.3% of patients who received bamlanivimab compared to 20.0% of patients who did not receive bamlanivimab (RR 0.37, 95% CI: 0.21-0.64, $p<0.001$.
- ICU admission was 2 vs. 5, NS.
- Total number of comorbidities (cumulatively input into the model as TNC) and the lack of receipt of bamlanivimab was found to be SS associated with hospitalization.
- However, the logistic regression model did not adjust for comorbidities or severity of illness at presentation, but only for race, gender and age.
- Some study authors were also funded by Eli Lily, the maker of bamlanivimab.
- This study has been met with significant criticism due to the inherent selection bias stemming from the patients who did show up for appointments or presented with more severe illness to the ED who comprised the control group. No attempt was made to adjust for these variables.
- Racialized patients were also more likely to not show up and hence the differences in socioeconomic status is underappreciated in this study.

Due to the significant biases, no conclusive result can be drawn from this study.

Various studies have since confirmed that common variants are resistant to bamlanivimab monotherapy, with only the B117 retaining susceptibility. The Public Health Agency of Canada synthesized the pertinent evidence into a table:

Table 1. Susceptibility/Resistance of SARS-CoV-2 variants to therapeutic interventions

last updated April 16th, 2021

			Variants of concern/interest					
Type of intervention	Manufacturer	Name of intervention	B.1.1.7 (UK variant)	B.1.351 (SA variant)	P.1 (BRA variant)	P.2 (BRA variant)	B.1.526 (New York	B.1.427/B.1.429 (California)
mAbs	Eli Lilly	bamlavimab (LY-CoV555)	Susceptible[1, 3, 7, 13, 17,19,23,24]	Resistant (fold-change >1000[1], >10[17]), [3, 4, 7, 13,19,23,24]	Resistant[3, 4, 10, 13,19] (fold-change >10[17])	Resistant[7]	Nd	Resistant[13,19,23]
		etesevimab (LY-CoV016)	Resistant (fold-change >4[2], 4.9[15], 3.22[17]), Susceptible[13]	Resistant (fold-change >4[2, 15], >10[17]), [5, 13]	Resistant[2*, 10, 13], (fold-change >4[15], >10[17])	Nd	Nd	Susceptible[22]
		bamlanivimab + etesevimab	Susceptible[13,20]	Resistant[13,20]	Resistant[13,20]	nd	Nd	Resistant[20]
	Regeneron	casirivimab (REGN10933)	Susceptible[1, 2, 3, 6, 15,16,17]	Resistant (fold-change >1000[1], >4[2], 76.3[6], 13[15], 44.6[16], 3.28[17]) Partially resistant[3]	Susceptible[2*] Partially resistant[3] Resistant[10] (fold-change 8.2[15], 142.8[16], 6.17[17])	Nd	Resistant[21]	Susceptible[16,22]
		imdevimab (REGN10987)	Susceptible[1,2, 3, 6, 15, 16,17]	Susceptible[2,3,6 ,15, 16,17] Resistant (fold-change >3.5[2])	Susceptible [2*,3,10,15,16,17]	Nd	Susceptible[21]	Susceptible[16,22]
		REGN-CoV-2 (combination of REGN10933 + REGN10987)	Susceptible[6, 16,18]	Partially resistant(fold-change 9.1[6]), Susceptible[16,18]	Susceptible[16,18]	Nd	Susceptible[21]	Susceptible[16,18]
	VIR + GSK	VIR-7831	Susceptible[11**, 14]	Susceptible[11**, 14]	Susceptible[11**, 14]	Susceptible[11**]	Nd	Susceptible[22]
		VIR-7832	Susceptible[14]	Susceptible[14]	Susceptible[14]	Nd	Nd	Nd

EUA revoked: On March 18, the US Department of Health and Human Services halted the distribution of bamlanivimab monotherapy to California, Arizona and Nevada, stating that its wide-spread use may be driving the development of COVID-19 variants, particularly B 1.427 and B 135. A laboratory study cited that there was a 6.7-fold decrease in antibodies in the blood of seven out of eight people who had received treatment with monoclonal antibodies or convalescent plasma when infected with the new variants, attributing this to 'antibody escape'. https://www.sciencemag.org/news/2021/02/coronavirus-strain-first-identified-california-may-be-more-infectious-and-cause-more

On March 25, 2021 the company released a statement to say that they are no longer going to be manufacturing or distributing bamlanivimab monotherapy due to increasing presence of variants that are not susceptible to the drug.

On April 16, 2021, the FDA revoked the Emergency Use Authorization for bamlanivimab monotherapy. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab

On April 28, 2021, Health Canada issued a warning statement regarding the use of bamlanivimab monotherapy. While the approval order was not revoked, the warning cautions clinicians in administering the drug in jurisdictions where the prevalence of variants of concern is high. No definition or guidance is given regarding when precisely it should be avoided.

Regeneron (casirivimab/imdevimab)

The Regeneron cocktail also has a positive Phase II study showing positive results on viral load.

N Engl J Med 2021; 384:238-251 - REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

- A trial in January looking at two different doses showed that viral load was reduced, but clinical endpoints such as needing a hospital/ED visit were very low and not statistically significantly different between groups.
- An EUA has been in place due to these promising results. There are 6 current trials with this drug and recently the company released a statement that one of the trials was positive enough to apply for a license with.

Clinical Phase 3 evidence for casirivimab/imdevimab has also been recently published. The large trial evaluating two doses (1200mg and 2400mg) compared to placebo in outpatients with mild COVID showed modest, but statistically significant results in preventing the primary outcome of admission to hospital .

Weinreich et al (June 2021): REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients

Study Design: Phase 3 of an adaptive, randomized, double-blind, placebo controlled trial of high risk outpatients diagnosed with COVID-19, evaluating a single dose of Regeneron 2400mg vs. 1200mg vs. placebo in preventing a composite outcome of COVID-19 hospitalization and all-cause mortality.

Participants:

- Unvaccinated adult outpatients diagnosed with COVID-19 ≤72 hours prior to randomization with symptoms consistent with COVID-19 lasting 7 days or less. Median symptom duration at randomization was 3 days.
- Patients were included (N=4057) if they were deemed to be at high risk for hospitalization defined as having at least one risk factor such as age 50 or greater, or the presence of at least one comorbidity such as obesity, hypertension or diabetes if younger.
- Initially, patients without risk factors were also enrolled, however the trial's protocol was amended and these patients were no longer enrolled or included in the analyzed analysis. There was initially also an 8000mg dose; patients who received this dose were not included in the analysis after the protocol amendment.
- Mean age was 50 years old; 49% of patients were male, 35% were Hispanic. The most common risk factor was obesity (58%) followed by age over 50 (52%).
- Patients were assessed for the presence of SARS-COV2 anti-spike protein antibodies and the primary outcome result was stratified by Ab positive, negative or unknown. Patients were not excluded if they were seropositive. 69% of patients were sero-negative at baseline. Viral load from index NP swab was also measured and was a median of 6.98 log10 copies/mL which the authors characterize as a "high viral load".
- Patients were enrolled between Sept 24, 2020 and Jan 17, 2021 and followed for 28 days.

- It is not clear which countries this study took place; from the author's affiliations it appears patients were enrolled in the US and Mexico.

Primary Endpoint: Composite of COVID-19 related hospitalization (emergency room visits or urgent care visits were not considered hospitalizations) and all-cause death.

Results:

- In the 1200mg arm, 736 patients received the drug and 748 placebo. The primary endpoint occurred in 7 patients (1%) vs 23 patients (3.2%), equating to an ARR of 2.2% and an NNT of 50. In the 2400mg arm, 1355 patients received the study drug and 1341 placebo. The primary endpoint occurred in 18 patients (1.3%) vs. 62 (4.6%) for an ARR of 3.3% and an NNT of 30.
- The relative risk reduction of the primary endpoint was similar in both groups (70.4% and 71.3% respectively).
- The differences observed in the primary outcome was largely related to differences in COVID-19-related hospitalizations (Table S6). In the 1200 mg arm vs placebo, hospitalization was 0.8% vs 3.1%. For mortality, 1/736 and 1/748 patients died, respectively. In the 2400 mg arm vs placebo, hospitalization was 1.3% vs 4.4%. For mortality, 1/1355 vs 3/1341 patients died, respectively.
- Clinical efficacy was seen at day 3 where Kaplan-Meier time-to curves split between the treatment and placebo groups.
- Those who were seropositive experienced similar absolute and relative risk reductions (1.44% vs. 3.16%), 826 patients in the study were seropositive.
- There was also a 4-day reduction in COVID-19 related symptoms (10 vs 14 days).
- Viral clearance was measured as a secondary endpoint and occurred faster in the treatment population (6 days vs. 13 days). High baseline viral loads were associated with higher risk of hospitalization; lower viral loads were associated with a less profound impact of the study drug.
- Various other hypothesis testing outcomes were reported, for example hospitalization at certain time frames; most of them favoured the study drug.

Study Strengths:

- The Regeneron antibody cocktail retains activity against P1, B117, B135 and the California/NY strains and is not affected by variants of concern which increases the external validity of the study under current conditions.
- Recruitment did not appear to pose significant issues; patients who were recruited attended appointments and there was very little non-inclusion due to no-shows or declining to participate.
- Recruitment with respect to symptom onset and positive COVID-19 PCR mirrored what is seen in practice.
- The patient population was reasonably generalizable, including those who had common chronic diseases mainly DM, heart issues and obesity.
- While vaccinated individuals were excluded, the study did include over 25% of patients who were seropositive for SARS-COV2, likely due to rapid post-infection seroconversion Patients who were seropositive seemed to have the same ARR in treatment vs. placebo (1% vs. 3.9%) and were hospitalized at approximately the same rate as those who were seronegative. This is hypothesis generating and potentially relevant to patients who develop COVID-19 despite immunization and ineffective natural immunity.

- In terms of ADRs, they seem low and acceptable.
- There is a pathophysiological rationale for the results - viral load was associated with hospitalization; the drug lowered viral load and led to the primary outcome benefit.
- Seropositivity was not associated with either, which could mean that if symptoms were present despite humoral immunity, there may still be an additional benefit from the drug.

Study Limitations:

- Patients who were vaccinated were not included in the study. Those vaccinated have a much lower absolute risk of catching COVID-19 and subsequently becoming severely ill. While 25% of patients demonstrated the presence of antibodies, antibodies from rapid infection-related seroconversion are different from being seropositive (and having the more important cellular immunity) from a vaccine. As such, the performance of monoclonal antibodies in a fully vaccinated population remains to be evaluated.
- Certain high risk individuals were under-represented, for example elderly over 65 and patients who were immunocompromised (3% of the study population). Those receiving other monoclonal antibodies or steroids were excluded; it would be important to evaluate the efficacy of the drug in this population due to their high risk of poor outcomes and potentially suboptimal response to vaccination.
- There is no benefit on mortality even when thousands of patients are given the drug, which impacts the cost-benefit equation.
- This drug may not be cost effective at a current unofficial price of $1200 USD/dose. Factoring an NNT of 30, an average length of hospital stay of patients in the study of 6 days (with 1 in 4 patients being admitted to the ICU), a 4-day decrease of symptoms (assuming a 50% QoL improvement) and approximately $100/patient for administrative costs associated with the infusion, the cost/QALY would be an estimated $163,000. With no impact on mortality or length of stay, this does not meet the current thresholds for funding. A drug price of ~$300/dose would, however.

RECOVERY - Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

- A randomised, controlled, open-label platform trial, several possible treatments were compared with usual care in patients hospitalised with COVID-19 which evaluated the impact of REGN-COV on mortality, as with various other treatments.
- Between 18 September 2020 and 22 May 2021, 9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone. The REGEN-COV dose was 8g.
- 3153 (32%) were seronegative patients, 5272 (54%) were seropositive patients and 1360 (14%) were patients with unknown baseline antibody status.
- In the primary efficacy population of seronegative patients, 396 (24%) of 1633 patients allocated to REGEN-COV and 451 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio 0·80; 95% CI 0·70-0·91; p=0·0010).
- In an analysis involving all randomised patients (regardless of baseline antibody status), 944 (20%) of 4839 patients allocated to REGEN-COV and 1026 (21%) of 4946 patients allocated to usual care died within 28 days (rate ratio 0·94; 95% CI 0·86-1·03; p=0·17).

- Patients were not excluded on the basis of their vaccination status - based on the enrollment dates of the trial it is assumed that most patients were not fully vaccinated
- Patients were randomized as soon as feasible: RECOVERY did not verify serostatus at the enrollment phase but rather randomized patients without knowing their serostatus
- Patients' serology was batched and reported after REGN-COV or usual care was already administered. Results were stratified on the basis of seropositive, seronegative or unknown serostatus.
- Seronegative patients receiving oxygen drove the primary endpoint - the subgroup of critically ill or receiving organ support did not appear to benefit.
- Mortality was numerically higher in those who were seropositive, however this did not reach statistical significance.
- The OR for being discharged alive was 0.92, i.e. lower in the REGENERON arm, with a CI of 0.88-1.00, making it NS by only 0.01
- Meanwhile, the trial advisory board overseeing the manufacturer's own RCT halted their in-patient trial due to signals of harm. The drug is currently unapproved for use in inpatients and various other mAbs have warnings of potential harm in inpatients (e.g. sotrovimab)
- Due to the inability of quickly identifying seronegative patients and potential signals of harm in those who are seropositive, or inpatients in general, the use of REGN-COV in this population remains controversial and not recommended until more information is known.

Antibiotics

Recommendation:
Antibiotics should be initiated based on local institutional antibiograms and sensitivities if bacterial infection is suspected.

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:
Acetaminophen is recommended preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.

On March 17, 2020, 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:
Patients on ACE inhibitors and ARBs are recommended to 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).

SSRIs

Recommendation:
SSRIs are not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials..

Lenze Ej et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA 2020

Background

- Sigma 1 receptor (S1R) is an endoplasm reticulum chaperone protein with various functions, including regulation of cytokine production
- Fluvoxamine, strong S1R agonist, inhibited cytokine production in a mouse septic shock model

Design

- DB, PC, RCT
- Single location (greater St Louis, in eastern Missouri & southern Illinois)
- Recruited April 10-Aug.5, 2020. Follow up completed Sept 19.
- Remote, contactless trial
    - Data collection via BID REDCap email surveys (phone was backup if no email)
        - Adverse events, compliance
    - Patient self-assessed vitals with equipment delivered
    - Daily phone calls x 3 days, then case by case basis
- 1:1 randomization
- Fluvoxamine 100 mg po tid vs matching placebo x 15 days
    - 50 mg qhs x 1 dose, then 100 mg BID x 2 days then 100 mg tid as tolerated through day 15
    - Followed by optional open label phase fluvoxamine 100 mg BID x 3 days, then 50 BID x 3 days then stop

Inclusion

- Outpatients 18 years and older
- Proven SARS-CoV-2 positive by PCR
- One or more active symptoms: fever, cough, myalgia, mild dyspnea, diarrhea, vomiting, anosmia, ageusia, sore throat
- Ability to provide Informed consent

Exclusion

- Severe illness requiring hospitalization or already meeting primary endpoint for clinical worsening (O2 sats < 92% on RA)
- Unstable comorbidities including but not limited to severe underlying lung disease (COPD, on home O2, ILD, pulmonary hypertension), decompensated cirrhosis, HF (NYHA 3 or 4 per patient report or medical records)

- Immunocompromised (SOT, BMT, AIDS, on biologics or steroids equivalent to > 20 mg/day of prednisone)
- Enrolled in another COVID 19 trial, or taking chloroquine, hydroxychloroquine, azithromycin or colchicine
- Unable to provide consent (e.g. moderate to severe dementia)
- Unable to perform study procedures.

Other

- Research team evaluated concurrent prescription drugs, OTC meds and caffeine use to mitigate drug interactions.
- Patients on SNRI/SSRIs included if they can be safely switched over to fluvoxamine briefly.

Primary endpoint

- Time to clinical worsening. Clinical worsening was defined as both: (1) presence of dyspnea and/or hospitalization for shortness of breath or pneumonia, plus (2) decrease in O2 saturation (<92%) on room air and/or supplemental oxygen requirement in order to keep O2 saturation >92%. Determined by phone discussion and review of medical records.

Results

- 1337 screened, 181 randomized (14%) (834 excluded, 322 declined participation)
- 152 (of 181) started the study and used for analysis (20 excluded, 9 didn't start meds)
- 35 patients in open label phase but no data collection
- Mean age 46 years, 70% female, 70% white, majority (~80%) overweight or obese by BMI
    - Few comorbidities, asthma (~17%) , HTN (~20%), DM (~11%). Few patients with depression/anxiety (~7%)
- Median O2 sat 97% in both groups, range 92-99 in placebo group, 93-99 in fluvoxamine group
- Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 (8.3%) patients in the placebo group (absolute difference, 8.7% [95% CI, 1.8%-16.4%] by survival analysis, log-rank $\chi^2 = 6.8$ and P 0.009
    - 4 of 6 hospitalized, one ventilated
    - 6 patients who deteriorated had baseline O2 sats less than/equal to 96%
- Fluvoxamine – 1 serious adverse event (hospitalization for dehydration) and 11 other events, 6 serious and 12 other in placebo group
- 20% patients stopped responding to surveys (18 patients on fluvoxamine, 19 on placebo) – concluded this was random
- Within 30 days after day 15 (not pre-specified outcome)– one fluvoxamine admitted for headache, one placebo admitted for costochrondritis

Limitations

- Contactless (self-reporting, self measurements)
- Predominantly young, few comorbidities. Oldest patient was 75 years old.
- Unclear if everyone received target dose
- Unclear how drug interactions, switching antidepressants were handled
    - But few patients with psychiatric illness in study

- Short follow up

Conclusion

Preliminary findings, larger RCT needed

Recommendations

Corticosteroids

i) Non hospitalized patients with no oxygen requirements:
In adults with mildly ill COVID-19 aged 65 and over OR aged 50 and over with underlying health conditions and within 14 days of symptom onset, **inhaled budesonide** 800 µg twice daily for 14 days may be considered on a case by case basis in discussion with the patient by clearly highlighting the uncertainty in the benefit of treatment, and the risks and potential adverse effects. Informed consent should be obtained and treatment initiated as soon as possible. Underlying health conditions include weakened immune system due to illness or medication; heart disease and/or hypertension; chronic lung disease; diabetes; hepatic impairment; stroke or other neurological condition; obesity or BMI above 35.

ii) Hospitalized patients requiring oxygen or higher levels of respiratory support
Dexamethasone 6 mg IV/PO q24h for up to 10 days is strongly recommended (RECOVERY trial), unless higher doses are clinically indicated (e.g. asthma exacerbation, refractory septic shock, history of chronic steroid use, obstetric use for fetal lung maturation).
Hydrocortisone 50 mg IV q6h is recommended as an alternative (REMAP-CAP trial). If dexamethasone and hydrocortisone are not available, methylprednisolone 32 mg IV q24h or prednisone 40 mg PO daily are recommended.

Tocilizumab and sarilumab

T**ocilizumab 400mg IV (single dose) OR Sarilumab** 400 mg IV (single dose) is recommended (REMAP-CAP, RECOVERY) for patients requiring life support due to confirmed COVID-19. This includes high-flow oxygen support (e.g., Optiflow) if flow rate > 30 L/min and FiO2 > 0.4 OR invasive or non-invasive ventilation OR vasopressor or inotropic support. Tocilizumab or sarilumab must be administered within 24 hours of the initiation of life support measures. Patients admitted to hospital for more than 14 days with symptoms of COVID-19 should not receive tocilizumab or sarilumab for this indication. Tocilizumab or sarilumab should only be initiated when life support is required because of COVID-19 rather than other causes (such as bacterial infection, pulmonary embolism, etc.).

If tocilizumab is not available due to ongoing global shortages, baricitinib is recommended as an alternative. Baricitinib 4 mg po daily (for patients with GFR ≥ 60 mL/min) or 2 mg po daily (for patients with GFR 30-59 mL/min) or 2 mg po every 2nd day (for patients with GFR 15-29 mL/min) up to 14 days, or until discharge from hospital (whichever occurs first) is recommended (COV-BARRIER) for patients requiring life support due to confirmed COVID-19. This includes high-flow oxygen support (e.g., Optiflow) if flow rate > 30 L/min and FiO2 > 0.4 OR invasive or non-invasive ventilation OR vasopressor or inotropic support. Baricitinib should be administered within 24 hours of the initiation of life support measures. Baricitinib should only be initiated when life support is required because of COVID rather than other causes (such as bacterial infection, pulmonary embolism, etc). Baricitinib should not be administered to patients with neutrophils < 1.0 giga/L, lymphocytes < 0.2 giga/L, ALT or AST > 5 x ULN, or eGFR < 15 mL/min (or receiving renal replacement therapy).

*There are very limited data on baricitinib in pregnancy. Risks and benefits of baricitinib should be discussed on a case by case basis with pregnant women with severe COVID-19.

Tocilizumab is not recommended for patients receiving low-flow oxygen support. The RECOVERY trial found a survival benefit of 4% (tocilizumab 29% vs. usual care 33% 28-day mortality) in patients who had CRP ≥75 mg/L AND low-flow oxygen, non-invasive respiratory support, or invasive mechanical ventilation. However, considering the scarcity of IL-6 blockers in Canada, drug therapy should be prioritized to the persons with both the highest need and the greatest likelihood of benefiting from the therapy. Combined with outstanding issues in the preliminary findings of the RECOVERY trial (e.g. 17% of patients randomized to tocilizumab not receiving the drug), the CTC recommends prioritizing tocilizumab use only for critically ill patients at this time, which is the population shown to benefit in both the REMAP and RECOVERY trials.

Therapeutic anticoagulation and venous thromboembolism (VTE) prophylaxis

i) Hospitalized patients requiring low-flow oxygen:

Therapeutic anticoagulation (LMWH preferred) may be beneficial and therefore considered in patients without high risk features* for serious bleeding and NOT requiring organ support. If used, anticoagulation for COVID-19 should start within 72 hours of admission and continue for 14 days or until hospital discharge. Patients who decompensate and require organ support while on therapeutic anticoagulation should continue on therapeutic anticoagulation. Therapeutic anticoagulation was superior to standard of care for composite 21-day organ support free survival in the ATTACC/ACTIV-4a/REMAP-CAP trials. Benefits appear to be driven by reducing progression to high-flow oxygen, non-invasive ventilation, or vasopressors. There was insufficient certainty on whether therapeutic anticoagulation improves mortality or intubation. Therapeutic anticoagulation reduces thrombotic events (1.4% vs 2.7%) but may increase major bleeding (1.9% vs 0.9%). *High risk features for bleeding include: age 75 or greater, eGFR less than 30 mL/min, any coagulopathy, platelet count less than 50, use of dual antiplatelet therapy, recent history of serious GI bleed or recent intracranial condition (stroke, neurosurgery, aneurysm, cancer), epidural or spinal catheter.

ii) Hospitalized patients requiring organ support (high-flow oxygen, non-invasive ventilation, mechanical ventilation and/or vasopressor/inotropic support)

Prophylactic-intensity dosing of low molecular weight heparin (LMWH) is recommended for VTE prophylaxis in patients who do not have suspected or confirmed VTE (or other indications for therapeutic anticoagulation). There is a high probability of harm when therapeutic anticoagulation is initiated in patients who have received organ support for greater than 48 hours (n=1074; NIH mpRCT). **Patients receiving therapeutic anticoagulation** for COVID-19 **prior** to organ support should **REMAIN** on therapeutic anticoagulation and continue for up to 14 days or until hospital discharge.

Colchicine

In patients aged 40 years or older with PCR-confirmed COVID-19 who have at least one risk factor† and no contraindications††, colchicine 0.6 mg PO BID x 3 days, then 0.6 mg daily x 27

days may be considered on a case-by-case basis in discussion with the patient by clearly highlighting the uncertainty in the benefit of treatment, and the risks and potential adverse effects. Informed consent should be obtained and treatment initiated as soon as possible.

Remdesivir

Remdesivir has not demonstrated benefit in survival, progression to ventilation or length of hospital stay and remains uncertain with respect to shortening time to recovery by 5 days. The World Health Organization (WHO) has issued a conditional recommendation against the use of remdesivir in hospitalized COVID-19 patients. Further evaluation in approved clinical trials is strongly encouraged. If remdesivir is used outside of clinical trials, full disclosure of risks and benefits with consideration of patient values and preferences are necessary, as it is not considered standard of care. Furthermore, it should be restricted to hospitalized patients requiring supplemental oxygen but not requiring non-invasive or invasive mechanical ventilation.

Lopinavir / Ritonavir (Kaletra®)

Lopinavir/ritonavir is not recommended for treatment of COVID-19. Lopinavir/ritonavir is not recommended for prophylaxis of COVID-19 outside of approved randomized-controlled trials.

Chloroquine or Hydroxychloroquine

Chloroquine or hydroxychloroquine (with or without azithromycin) is not recommended for treatment or prophylaxis of COVID-19.

Oseltamivir

Oseltamivir is not recommended for treatment or prophylaxis of COVID-19.

Ribavirin and Interferon

Interferon IV/SC is not recommended for the treatment of COVID-19. Ribavirin/Interferon (Inhaled) is not recommended outside of approved clinical trials.

Ivermectin

Ivermectin is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

Ascorbic Acid and Vitamin D

Ascorbic acid and Vitamin D are not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

Convalescent Plasma[#]

Convalescent plasma[#] is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

Intravenous Immunoglobulin G

Intravenous immunoglobulin G (IVIG) is not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

Monoclonal Antibodies/Antibody Cocktails

i) Critically ill:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) are NOT recommended. An RCT of REGN-COV2 in this population was halted due to signals of harm. Regdanvimab conditions for use state that it may be associated with worse outcomes in the critically ill. RECOVERY showed no benefit in the subgroup that required organ support. Various guidelines (IDSA, NIH, INESSS) recommend against mAbs in this setting.

ii) Severely ill:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) are not recommended. MAbs have shown inconsistent results in RCTs. TICO was stopped for futility as mortality was numerically higher in the Bamlanivimab arm. RECOVERY demonstrated a mortality benefit with REGN-COV2, but only in seronegative patients, with signals of harm in seropositive patients. Reliable rapid antibody tests to identify the target population are not readily available and all mAbs remain unapproved in Canada for in-patients with COVID-19.

iii) Mildly ill:

Monoclonal antibodies (mAbs; Bamlanivimab/etesevimab, REGN-COV2, Sotrovimab, Regdanvimab) IV have shown to reduce hospitalization rates (although not mortality or length of stay) in UNVACCINATED outpatients at high-risk of complications due to comorbidities (age >40 with a comorbidity like obesity or hypertension). Due to high vaccination rates and barriers to operationalizing outpatient IV administration outside of clinical trials, the clinical application of these studies is limited. **mAbs may be considered on a case-by-case basis in those inadequately immunized (unimmunized, partially immunized or inadequate immune response) with mild disease AND who are at high risk of developing severe COVID-19-related complications.** The subcutaneous route has shown similar reductions in viral loads, but clinical data is lacking and would still present operational barriers such as multiple injections and required observation time.

iv) Prophylaxis:

Bamlanivimab/etesevimab IV has shown to reduce the development of symptomatic COVID-19 as prophylaxis in unvaccinated LTC residents, as has subcutaneous REGN-COV2 given to unvaccinated, seronegative, PCR-negative household contacts if given within 96 hours of exposure. Due to lack of reliable rapid tests to identify the target population within the prophylaxis window, lack of impact on hospitalization rates or mortality and low generalizability of these studies, **mAb administration is not recommended for post-exposure prophylaxis**.

Antibiotics

Antibiotics should be initiated based on local institutional antibiograms and sensitivities if bacterial infection is suspected.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Acetaminophen is recommended preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.

Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs)

Patients on ACE inhibitors and ARBs are recommended to continue these agents as indicated and not cease therapy solely on the basis of COVID-19.

SSRIs

SSRIs are not recommended for treatment or prophylaxis of COVID-19 outside of approved randomized-controlled trials.

Other investigational therapies

Other investigational agents including arbidol, ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab, famotidine, niacin, thymosin, natural health products and traditional Chinese medicines are not recommended for treatment or prophylaxis of COVID-19 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

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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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Please refer to in-text hyperlinked references

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