Key Research Question:

What is the evidence for and risks of using hydroxychloroquine (HQ) as a treatment and prophylaxis for SARS-CoV-2? [Updated April 16, 2020]

Context

- There is widespread concern of contracting the virus that causes COVID-19 among both the public and among health care workers.
- HQ has been suggested as treatment and prophylaxis for COVID-19 illness in social media, news reports, some scientific data and announcements from politicians.
- In Alberta, there have been anecdotal reports of physicians prescribing HQ for their colleagues or staff. This has prompted an advisory from the Alberta College of Pharmacy for their members not to dispense HQ when stockpiling is suspected (Alberta College of Pharmacy, March, 2020). A similar advisory was sent from the College of Physicians and Surgeons of Alberta to its members (April 2020).
- There is ongoing controversy about the role of HQ in the treatment of COVID with evolving signals of potential harm in COVID-19 patients. Recommendations that HQ be taken off order sets for COVID management in AHS outside the setting of monitored randomized controlled trials have been made to reflect changes to major national guidelines (Association of Medical Microbiology and Infectious Diseases Canada, Infectious Diseases Society of America, American Thoracic Society) in Canada and the US.

Key Messages from the Evidence Summary

- The evidence of HQ effectiveness in treating COVID-19 illness is limited. Although there is plausible in vitro activity of HQ against COVID-19, there is equivocal in vivo data across observational studies and small randomized controlled trials with significant methodologic concerns.
- There is no evidence for HQ for use as prophylaxis for COVID-19 illness. There are multiple randomized trials underway to explore this in health care workers and close contacts to known cases.
- HQ risks, particularly when used for patients with cardiopulmonary compromise due to COVID-19 infection, include the potential for serious clinical and laboratory adverse effects, potential drug interactions, and carry a risk to children if unintentionally ingested.

Committee Discussion

The committee recommended prioritizing use of HQ for patients with rheumatologic disease, and those in COVID-19 randomized controlled clinical trials and recommended removing HQ from COVID-19 order sets. The committee felt strongly that any off-label use of HQ requires the prescribers’ careful consideration of risk/benefit, consultation between experts and attending physicians, and documenting a verbal consent from patients after discussion of the current state of the evidence.
of evidence of benefit and harms. This reflects the content of an Ethics consult that was done in the context of this review. Committee members noted that if used outside the context of clinical trials, adverse events of HQ for hospitalized patients should be documented/collected by clinicians through the AHS Reporting and Learning System for Patient Safety at https://insite.albertahealthservices.ca/tools/rls/Page1820.aspx. One committee member felt strongly that HQ should not be used outside the context of a clinical trial. It was noted that the HOPE Alberta COVID trial is collecting information on the safety of HQ at 7 and 30 days in trial participants.

There were concerns raised by the Divisions of Infectious Diseases regarding continuation of the recommendation for mandatory Infectious Disease (ID) consult or approval, because of the variation in opinion of ID physicians on off label investigational therapies in COVID-positive patients. Therefore, we recommend to remove this from the existing process and instead leave it as an option on a case by case basis reflecting usual clinical considerations. Since an option of using HQ for hospitalized patients will still exist, it is important to prescribers to determine the risk of adverse events prior to initiation. This includes ensuring physicians are aware of and mitigate the risk of prolonged QTc (including ordering baseline ECG, and assessing drug interactions with patient’s existing medications) and hypoglycemia. Pharmacy Services will be in a position to assist with the drug interaction check. The committee also felt that the additional safety concerns that exist for azithromycin and HQ, while specifically note in literature because these have been recommended for COVID19 in the past, are similar for all macrolides as the QTc prolongation is a class effect (i.e. same would happen with clarithromycin or erythromycin).

With respect to prophylaxis, there was agreement with the recommendation to restrict use of HQ for prophylaxis to only within clinical trials as there is no existing evidence to support benefit, and there are concerns with increased household use of hydroxychloroquine given concerns around risk and toxicity to children who might unintentionally access this within the home setting.

**Recommendations**

1. Hydroxychloroquine is not currently recommended to be used as prophylaxis for COVID-19 outside clinical trials, given the lack of established benefit to counterbalance potential harms, and no existing data on prophylaxis.

2. Given the significant increased risk of QT prolongation and cardiac arrhythmias, HQ should not be used with azithromycin or other macrolide antibiotics unless in the context of a clinical trial. These medications should also not be used sequentially given very long half-lives and continued QT prolongation risk.

3. As there are limited supplies of hydroxychloroquine within AHS, and concerns may eventually arise with supply in Alberta’s community pharmacies, its use should be prioritized to those patients who are on it for chronic rheumatologic conditions, where there is stronger evidence of benefit.
4. For patients with COVID-19 disease, in both the hospital and the community, preference for use of HQ as treatment is given to those enrolled in clinical trials investigating the effects of HQ in treating and preventing severe COVID-19 illness.

5. Off-label prescribing of hydroxychloroquine for treatment of COVID-19 positive inpatients should only be performed after careful consideration of the potential harms, consideration of expert consultation as needed (e.g., Infectious Disease, Respiratory Medicine, and General Internal Medicine) and discussion between the Most Responsible Physician and the patient.

6. If all criteria in #5 are met and the decision is made to use HQ:

   a. The use of a risk stratification tool (e.g. Tisdale et al, 2013) to access the risk of QTc prolongation must be considered when evaluating the benefit vs harm of using HQ as treatment in SARS-CoV-2 patients.

   b. A drug interaction check between HQ and the patient’s medications must be completed using the website [https://www.covid19-druginteractions.org/](https://www.covid19-druginteractions.org/) or a suitable alternative. Pharmacy Services can assist with performing the drug interaction check.

   c. While the patient is on HQ, baseline and intermittent ECGs to assess the corrected QT (QTc) interval during treatment should be considered depending on the patient’s baseline risk.

   d. Adverse events with respect to off-label use of HQ for inpatient treatment should be documented and reported by clinicians through the AHS Reporting and Learning System for Patient Safety at [https://insite.albertahealthservices.ca/tools/rls/Page1820.aspx](https://insite.albertahealthservices.ca/tools/rls/Page1820.aspx).

   e. These recommendations will be updated as the published data evolves.

Summary of Evidence

Literature for this rapid review was gathered in a search strategy performed by Knowledge Resource Services (KRS) in AHS, pulling from a pragmatic search of the COVID-19 literature, as well as through medication safety sources (e.g.: LexiComp). Limitations to this review are the lack of available scientific peer reviewed evidence on this topic for COVID-19 and there may be evidence from the SARS and MERS experience that was missed by this strategy. A total of 61 references were included in this review. Inclusion/exclusion criteria can be found in the Appendix.

What is the evidence that HQ is effective as a treatment for COVID-19?

In Vitro

Both chloroquine (CQ) and HQ have been shown in vitro to inhibit the growth of coronavirus (Keyaerts et al., 2004; Liu J et al, 2020; Vincent et al., 2005; Kono et al., 2008; Yao et al., 2020; Wang et al., 2020). Yao (2020) and Wang (2020) are already referenced in the Alberta Health Services (AHS) antimicrobial recommendations document (AHS, 2020). In summary, in vitro studies show a plausible role of HQ in the treatment of SARS-CoV-2.
Hydroxychloroquine as treatment/prophylaxis for COVID-19

In Vivo

*In vivo* studies in mice have also shown that CQ improves survivability in mice infected with human coronavirus (Keyaerts et al., 2009). With respect to human studies, the first clinical trial data became available mid-March from an open label nonrandomized trial, looking at the efficacy of 600 milligrams of hydroxychloroquine twice a day (plus/minus azithromycin) in reducing nasal swab viral burden by polymerase chain reaction (PCR) positivity in a cohort of 20 patients. At days 3 and 6 post-therapy, PCR was negative in 50% and 70% of the treated patients, respectively, compared to 6.3% and 12.5% in the untreated group (Gautret et al., 2020a). No clinical outcomes were reported, and patients with severe illness in the HQ arm were censored from the data after ICU admission. A small pilot randomized controlled trial in China (n=30) showed no difference in virologic or clinical patterns between HQ treated and untreated patients (Chen J, et al, 2020). A preprint randomized parallel-group trial of 62 patients reported that patients in the treatment arm (5-day HQ 200mg b.i.d.) had a significantly shortened body temperature recovery time (3.2 days [1.3 SD] vs 2.2 days [0.4 SD]; p=.0008) and cough remission time (3.15 days [1.5 SD] vs 2.0 days [0.2]; p=.0016) and improved pneumonia (80.6% vs 54.8%) (Chen Z et al, 2020). Notably, the original trial registered for this study included a sample size of 100 per group, with only 31 patients per group being reported (Chinese Clinical Trial Registry (ChiCTR), identifier: ChiCTR2000029559).

In summary, these studies provide some preliminary evidence that HQ may be effective in treatment of COVID-19; however, severe limitations and criticism of the Gautret et al (2020a) study are well known (Dahly D, Gates S & Morris T, 2020; Frie, K, & Gbinigie K, 2020; Kim et al, 2020; Lowe D, 2020; Retraction Watch, 2020; Yazdany & Kim 2020), and the Chen study was underpowered. Thus further evolution of this evidence is required.

Current State of Recommendations in Other Jurisdictions

Recommendations for the use of CQ/HQ in SARS-CoV-2 patients have been released beginning in China with respect to pulmonary disease (Dong et al., 2020, Gao J, Tian Z & Yang X, 2020; Liang et al., 2020) but there are recommendations in support of its use available internationally, including an Emergency Use Authorization issued by the US FDA on March 28, 2020 (Hinton, 2020, US FDA 2020a; US FDA 2020b). To date, recommendations are based on these *in vitro* data, limited and weak human studies and physician opinion rather than on clinical trial evidence. As such, recommendations for the use of HQ in SARS-CoV-2 patients would have to be made in the absence of high-quality clinical trial evidence at this time. Recently released guidelines for COVID-19 therapy from the Infectious Diseases Society of America,(IDSA, 2020) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach concluded that the currently available best evidence failed to demonstrate or exclude a beneficial effect of HQ on the clinical progression of COVID-19, noting that current trials assess only indirect outcomes. Very high risk selection bias was noted in the virologic outcomes described from HQ plus azithromycin use. Two studies described significant QT prolongation in 10 of 95 patients (Chorin et al, 2020; Molina et al, 2020).

What is the evidence that HQ is effective as a prophylaxis for COVID-19?

As of April 13, 2020, there are no available data from randomized clinical trials, cohort or observational studies to inform clinical guidance on the use, dosing, or duration of CQ or HQ for
Hydroxychloroquine as treatment/prophylaxis for COVID-19  • 5

prophylaxis of SARS-CoV-2 infection (Clinicaltrials.gov, 2020). A document circulating on Twitter indicates that HQ is being used for COVID-19 prophylaxis in India, using its purported benefits as a treatment as the rationale for prophylaxis (Bargahva, 2020). There is insufficient evidence on the effectiveness of HQ as a prophylactic for COVID-19.

**What are the risks of using HQ as prophylaxis or as treatment for COVID-19?**

In addition to the fact that RCTs are lacking, making it difficult to quantify risks in this specific uninfected population, the risks for HQ prophylaxis for SARS-CoV-2 include the following:

1. Acute adverse effects may include serious clinical and laboratory features, including prolonged QTc and hypoglycemia.
2. Multiple potential drug interactions with patient’s therapeutic medications.
3. Risk of pediatric morbidity and mortality with increased unintentional exposures in the home if used widely for prophylaxis.

Safety considerations for the use of CQ, HQ and AZM and other macrolide antibiotics in the management of SARS-CoV-2 infections identified the potential risks of treatment using CQ/HQ to include QTc prolongation (Chorlin et al, 2020), particularly in patients with pre-existing cardiac disease or if used in combination with AZM, as well as other known risks associated with these drugs including hypoglycemia (Unübol M et al, 2011), drug-drug interactions (Somer M et al, 2000) and neuropsychiatric effects (Bhatia 1991; Das P et al, 2014). Evidence of adverse events is now available, including a preprint retrospective study that reported significant QTc prolongation (p<.001) in patients treated with a combination of HQ/Azithromycin, with the QTc in 11% patients increasing to >500ms (Chorin, E et al, 2020). In this study, both baseline QTc and QTc >460ms were not reliable predictors of extreme QTc prolongation in this preliminary work. Risk of pediatric morbidity and mortality with unintentional exposures is also concerning (Smith & Klein-Schwartz, 2005).

With respect to CQ, a parallel, double-blind randomized trial in Brazil on CQ as treatment for SARS-CoV-2 was required to shut down recruitment to the high dose arm (CQ 600mg b.i.d. for 10 days (total CQ=12g) due to fatal cardiac complications (13.5%) (Silva Borba et al, 2020).

**How stable is the supply of HQ to Alberta?**

HQ is an oral tablet is offered by four manufacturers in Canada. Overall there is a commitment to ensure continued supply at historical rates to ensure continued access for patients on HQ for other conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis). With the worldwide focus on HQ use in COVID-19, it is anticipated that supplies beyond historical use will be limited and inappropriate use will result in reduced access for patients with chronic rheumatologic conditions such as lupus and rheumatoid arthritis that require ongoing maintenance therapy.

While AHS can directly assess its current HQ stock, this is not possible for community pharmacies.
Evolving Evidence
The evidence for these research questions is rapidly evolving. There are several clinical trials underway investigating the prophylactic and treatment effectiveness of HQ. This review will be updated as new data from additional trials is made available. It will be important to be able to assess the quality and outcomes of these upcoming human clinical trials to understand the efficacy of HQ in COVID-19.

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Authorship & Committee Members
This review was updated by Jamie Boyd and scientifically reviewed by Mark Yarema (external reviewer), Braden Manns (co-chair), and Riley Hartmann (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Lynora Saxinger (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

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Appendix

List of non-clinical abbreviations
AHS: Alberta Health Services
AZM: Azithromycin
CalHR: Calibrated hazard ratio
CQ: Chloroquine
CIOMS: Council for International Organizations of Medical Sciences
HQ: Hydroxychloroquine
RCT: randomized controlled trial

Inclusion and Exclusion Criteria for Studies Eligible for Data Extraction

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<td>• HQ as treatment or prophylactic for COVID-19</td>
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<td>• Describes coordination of research efforts for use of HQ in COVID-19 cases</td>
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<td>• Article is peer-reviewed, is from a reputable source, or has a described methodology (includes letters, abstracts, reviews)</td>
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* Letters to the editor and commentaries were reviewed for primary sources.

Evidence Review

Literature for this rapid review was gathered in a search strategy performed by Knowledge Resource Services (KRS) in AHS, pulling from personal literature libraries and a pragmatic search of the COVID-19 literature. This is an important limitation of this review, as there may be
What is the evidence that HQ is effective as a treatment for COVID-19?

Findings from previous in vitro studies on a different corona virus, SARS-CoV, have suggested that chloroquine and hydroxychloroquine may inhibit the coronavirus through a series of steps. The drugs can inhibit glycosylation of the ACE2 receptor required for viral fusion to the cell membrane (Vincent et al., 2005). Additionally, it can change the pH of endosomes, causing further interference with cell fusion, along with inhibition of nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, virus release to achieve its antiviral effects.

In Vitro

There are in vitro studies for the use of CQ and HQ to inhibit SARS-CoV-2, such as Wang et al (2020) reporting that CQ in vitro showed antiviral activity in simian kidney cells at dosages and concentrations typical of chronic rheumatoid arthritis patients (Mackenzie, 1983). Lui et al (2020) reported that both CQ and HQ were potent compounds against viral particles finding comparable 50% cytotoxic concentration, with CQ having a lower 50% maximal effect than HQ. Whereas Yao and colleagues (2020) reported that HQ was stronger than CQ in vitro. The authors used in vitro data and theoretical physiologically based pharmacokinetic models to predict that these molecules will work in humans at the recommended dose. These two in vitro studies (Yao et al, 2020; Wang et al, 2020) are already referenced within the AHS COVID-19 antimicrobial recommendations document (AHS, 2020).

A Belgian study demonstrated that CQ demonstrated both antiviral and cytostatic activity in SARS-CoV-cultured cells (Keyaerts et al, 2004), which was also demonstrated in a study from the United States (Vincent et al, 2005). Vincent et al. also commented that CQ was effective both before and after the cells were cultured with the virus, and suggested a potential role for CQ in prophylaxis. One Japanese study also demonstrated CQ's ability to inhibit viral replication in human coronavirus 229E-infected cells (Kono et al, 2008).

In Vivo

There is one animal study from Belgium that demonstrated that CQ improved survival in mice infected with human coronavirus OC43 (Keyaerts et al, 2009).

Human trials

With respect to human trials, the first clinical trial data became available mid-March from an open label nonrandomized trial was published looking at the efficacy of 600 milligrams of hydroxychloroquine twice a day (plus azithromycin) in reducing nasal swab polymerase chain reaction (PCR) positivity in a cohort of 20 patients (Gautret et al, 2020a). At days 3 and 6 post-therapy, PCR was negative in 50% and 70% of the treated patients, respectively, compared to 6.3% and 12.5% in the untreated group (Gautret et al., 2020a). No clinical outcomes were reported, and patients with severe illness in the HQ arm were censored from the data after ICU admission. This study has been widely criticized including lack of randomization, handling of
patients lost to follow-up (patients excluded without intention to treat analysis), insufficient sample size to reach 85% power and absence of clinical outcomes reported (Dahly D, Gates S & Morris T, 2020; Frie, K, & Gbinigie K, 2020; Kim et al, 2020; Lowe D, 2020; Retraction Watch, 2020; Yazdany & Kim 2020). The results of this study built upon a February 2020 news briefing from China that reported clinical results in 100 patients showing reduced duration of illness and significant improvement in CT imaging following treatment with chloroquine phosphate, with no adverse events reported (Gao J, Tian Z & Yang X, 2020). Importantly, these findings seem to be a combination of ongoing clinical trials with varied study design and, to date, there is no empirical evidence available to confirm these findings.

Other human trials include a small pilot randomized controlled trial in China (n=30) which showed no difference in virologic or clinical patterns between HQ treated and untreated patients (Chen J, et al, 2020). A small, preprint randomized parallel-group trial of 62 patients with SARS-CoV-2 and chest CT confirming pneumonia found that, compared to the control group, the 31 patients in the HQ treatment arm (5-day HQ 200mg b.i.d) showed a significantly shortened body temperature recovery time (3.2 days [1.3 SD] vs 2.2 days [0.4 SD]; p=.0008) and cough remission time (3.15 days [1.5 SD] vs 2.0 days [0.2]; p=.0016), with a larger CT improvement seen in the treatment arm compared to the control arm (80.6% vs 54.8%, respectively) (Chen Z et al, 2020). Patients with any cardiac arrhythmia were excluded. 4 patients in the control group progressed to severe illness. In the treatment group, 2 patients experienced mild adverse effects (1 headache, 1 rash). Notably, the original trial registered for this study included a sample size of 100 per group, with only 31 patients per group being reported (Chinese Clinical Trial Registry (ChiCTR), identifier: ChiCTR2000029559).

As of April 13, 2020, there are 43 studies registered on Clinicaltrials.gov to examine the effectiveness of HQ in the treatment of SARS-CoV-2, of which two have a large focus on prophylaxis but are listed as treatment trials.

**Cohort and Observational Studies**

In response to the findings of Gautret et al (2020a), a small prospective study tested the virologic and clinical outcomes of SARS-CoV-2 patients treated with a combination of HQ (600mg/d for 10 days) and AZM (500mg day 1, 250mg days 2 to 5) (Molina et al, 2020). Of the 11 patients, treatment was discontinued in 1 patient due to QT prolongation, 1 patient died and 2 were admitted to ICU. Overall, 8 out of 10 patients (80%, 95% CI: 49 94) had nasopharyngeal swabs still testing positive for SARS-CoV-2 RNA at study day 5 to 6. HQ and AZM showed no difference in this study, contrasting the findings of the Gautret and colleagues study (2020a).

A follow-up observational cohort study by Gautret and colleagues (2020b) examined the efficacy of HQ in combination with AZM in 80 SARS-CoV-2 patient. Patients were included in the analysis if they received treatment for at least 3 days with follow-up for at least 6 days. Treatment offered to patients without contraindications was HQ at 200mg 3 times per day for 10 days & AZM at 500mg on day 1, followed by 250mg/day for the next 4 days. Of the included patients, 81.3% showed clinical improvement on a combination treatment of HQ & AZM, 15% required oxygen therapy, 3 patients were admitted to ICU and one 86yo patient died in the Infectious Disease unit. The authors conclude that there is “efficacy” for the use HQ in
combination with AZM for the treatment of COVID-19 (Gautret et al, 2020b). Notably, no control group was used in this study. As observational studies do not equate to determining efficacy, the findings are overstated by the authors.

There is a new unpublished abstract just released by the same research group as the Gautret studies (2020a; 2020b) that reports a cohort study of 1,061 patients treated with a combination of HQ and AZM for at least 3 days with 9 days follow-up found virological cure in 91.7% of patients with 4.3% of patients experiencing poor outcomes (ICU admission n=10; hospitalization longer than 10 days n=31; and death n=5) (Marseilles IHU group, 2020). Older age (OR 1.11) and initial severity (OR 10.05) were associated with poor clinical outcomes. Currently there is no manuscript available to assess study quality or examine data and outcomes, however as this study lacks a control group it contains the same limitations of other observational studies in that it does not determine efficacy.

Further, a new preprint study examining the effectiveness of HQ in SARS-CoV-2 patients (n=181) with pneumonia and oxygen requirements of ≥2L/min used routine clinical data to emulate a target trial. No difference were found between the treatment group (n=84; HQ at 600mg/d started within 48 hours of hospitalization) and the control group (n=94; no HQ for first 48 hours of hospital admission) in either transfer to ICU within 7 days (20.2% vs 22.1%, respectively; relative risk [RR]: 0.91, 95%CI: 0.47, 1.80) or mortality within 7 days (2.8% vs 4.6%; RR: 0.61, 95%CI: 0.13, 2.89) (Mahévas et al, 2020). Notably, HQ was discontinued for eight patients in the treatment group due to changes in their electrocardiogram (ECG).

Current State of Recommendations in Other Jurisdictions

The early ‘findings’, in combination with anecdotal perspectives, spurred several regions (CDC MICC Team, 2020; Hinton, 2020; Mount Sinai, 2020; Multicenter Collaboration Group, 2020; Sciensano, 2020) to support the use of CQ/HQ in SARS-CoV-2 patients, despite a severe paucity of evidence to support the effectiveness and safety of these medications within this population. There are several published letters (Dong et al, Gao et al) and a Handbook for diagnosis and management of COVID-19 from China (Liang et al). All of these recommend chloroquine as part of treatment for established COVID-19 pulmonary disease based on the recent experience of physicians in that country. A recent review on HQ in patients with diabetes in India concluded that HQ could be used with careful consideration in this population (Singh et al, 2020).

On March 28, 2020 the US FDA approved an Emergency Use Authorization for the use of CQ and HQ in SARS-CoV-2 patients (Hinton, 2020, US FDA 2020a; US FDA 2020b). Mount Sinai Health System has released treatment guidelines for use of HQ in COVID-19 patients stating that Infectious Disease (ID) consultation is available for COVID-19 patients but ID approval to prescribe HQ and AZM for treatment is not required (Mount Sinai, 2020). Conversely, European guidelines on the use of HQ in critically ill patients states there is insufficient evidence to recommend the use of CQ or HQ in critically ill adults with SARS-CoV-2 (Alhazzani et al, 2020). Insufficient evidence is also reported by several others (Agency for Care Effectiveness, 2020; Lenzer, 2020; Lowe D, 2020; Mc Cormack, 2002; Sciensano, 2020; Yazdany & Kim, 2020).
The American Heart Association, American College of Cardiology, and heart Rhythm Society have recommended that HQ and azithromycin be withheld in patients with baseline QT prolongation.

**What is the evidence that HQ is effective as a prophylaxis for COVID-19?**

The aforementioned *in vitro* studies do suggest potential benefit for HQ as a prophylactic for SARS-CoV-2 (Lui et al, 2020; Mackenzie, 1983; Wang et al, 2020; Yao et al, 2020). As of April 13, 2020, there are no available data from randomized clinical trials, cohort or observational studies to inform clinical guidance on the use, dosing, or duration of chloroquine (CQ) or hydroxychloroquine (HQ) for prophylaxis of SARS-CoV-2 infection.

There are 21 clinical trials registered on clinicaltrials.gov whose purpose is to study the effectiveness of CQ or HQ prophylaxis in healthcare workers or household contacts of people known to be COVID-19 positive.

There is a document circulating on Twitter that indicates that India has approved HQ prophylaxis for healthcare workers and household contacts in that country (Barghava, 2020). It appears that the rationale for approving it for prophylaxis is an extension of its benefits when used in treatment. Reports of toxicity have also circulated (see next Section).

In summary, there are no data to support the use of HQ as a prophylactic in SARS-CoV-2 patients. In the setting of known potential harms, HQ for SARS-CoV-2 prophylaxis should be avoided until there is quality trial data available (Kim et al 2020, Yazdany & Kim, 2020).

**What are the risks of using HQ prophylactically or as treatment for COVID-19?**

Since an early, now highly criticized, study (Gautret et al, 2020a) suggested that a combination of HQ and Azithromycin (AZM) resulted in improvement of clinical outcomes and viral loads in SARS-CoV-2 patients, many jurisdictions and clinicians have adopted the regimen; however, there is insufficient evidence to support this treatment combination in SARS-CoV-2 patients.

A new user cohort study (n=351,956) examined the risk associated with the addition of AZM to HQ treatment in patients with rheumatoid arthritis to guide decision making during the COVID-19 pandemic. The study reported an increased risk of 30-day cardiovascular mortality (calibrated hazard ratio [CalHR] 2.19 [95% CI 1.22, 3.94]), chest pain/angina (CalHR 1.15 [95% CI 1.05, 1.26]), and heart failure (CalHR 1.22 [95% CI 1.02, 1.45]) (Lane et al, 2020).

In SARS-CoV-2 patients, a preprint retrospective study of 84 consecutive adult patients found significant QTc prolongation (p<.001) in patients treated with a combination of HQ/Azithromycin, with the QTc in 11% patients increasing to >500ms (Chorin, E et al, 2020). In this study, both baseline QTc and QTc >460ms were not reliable predictors of significant QTc prolongation.

A case study of a comorbid 70yo female initially treated for community-acquired pneumonia describes that following a positive test for SARS-CoV-2, the patient was prescribed HQ starting 1 day after AZM and ceftriaxone were discontinued. The patient suffered ventricular fibrillation and cardiac arrest on day 5 of HQ due to QTc prolongation from a combination of HQ and AZM. HQ was prescribed after stopping AZM; however, it is suspected that the long half-life of AZM would put concentration still near or at therapeutic concentration (ISMP, 2020).
Further, a parallel, double-blind randomized Phase IIb clinical trial (ClinicalTrials.gov, number NCT04323527) run out of Brazil examining CQ use in SARS-CoV-2 patients was forced to shut down recruitment due to fatal cardiac complications in the high dose group, the dosing level recommended by Chinese guidelines (no in-text citation provided in current preprint) (Silva Borba et al, 2020). A total of 81 patients were enrolled into the trial (virological confirmation n=40; clinical-epidemiological suspicion n=41). Patients randomized to the low CQ dose arm received 400mg for 5 days, b.i.d. only on day 1 (total CQ= 2.7g) and the high CQ dose arm received 600mg b.i.d. for 10 days (total CQ = 12g). All patients were given azithromycin and ceftriaxone. Patient characteristics were similar between each group apart from all patients >75yo (n=5) were enrolled in the high dose arm. In the intention to treat population until Day 6 showed no differences in either safety outcomes (QTc prolongation [using Fridericia’s formula], increased creatinine, decreased hemoglobin or ventricular tachycardia) or efficacy outcomes including death, admission to ICU, need for inotropics, oxygen support needed, invasive mechanical ventilation or naso/oropharyngeal swab viral clearance which was measured on Day 4. The fatality rate until Day 6 was 13.5% (95%CI: 6.9, 23.0%; n=11) with a trend of higher fatalities in the high dose group. Due to these findings, the high dose arm of the study was interrupted to unmask and transition patients to the low dose arm. The authors conclude that treatment with high dose CQ for 10 days is not sufficiently safe and should no longer be used in severe SARS-CoV-2 patients (Silva Borba et al, 2020).

Safety considerations for the use of CQ, HQ and AZM or other macrolide antibiotics in the management of SARS-CoV-2 infections identified the potential risks of treatment using CQ/HQ to include QTc prolongation (Chorlin et al, 2020), particularly in patients with pre-existing cardiac disease or if used in combination with AZM, as well as other known risks associated with these drugs including hypoglycemia (Unübol M et al, 2011), drug-drug interactions (Somer M et al, 2000) and neuropsychiatric effects (Das P et al, 2014). Although in vitro studies and low quality human studies suggest the use of CQ/HQ in the treatment and prevention of SARS-CoV-2, clinicians and patients should be aware of the potential risks associated with this treatment, particularly in the absence of high quality evidence of this treatment within humans (Juurlink, 2020). Use of a tool (Tisdale et al, 2013) to access the risk of QTc prolongation must be considered when evaluating the benefit vs harm of using HQ as treatment in SARS-CoV-2 patients.

General Considerations regarding HQ use

Given that HQ is more readily available in Canada, the focus of this section is on HQ. Moreover, CQ is 2-3 times more toxic than HQ in animal studies, hence the use of CQ for malaria prophylaxis and HQ as an anti-inflammatory for patients with lupus or rheumatoid arthritis.

The daily doses of HQ in the trials listed above range from 200 to 600 mg/day for 4 days. In two of the trials, a loading dose of 800 mg X 1 dose precedes the daily dose. This is the same as the current treatment dose as described in the AHS COVID-19 antimicrobial treatment document (AHS, 2020).

1. Adverse effects
The following Council for International Organizations of Medical Sciences (CIOMS) frequency rating for adverse effects is used, when applicable:

- Very common: ≥ 10%
- Common: ≥ 1 and <10%
- Uncommon: ≥ 0.1 and < 1%
- Rare: ≥ 0.01 and <0.1%
- Very rare: < 0.01%
- Not known: frequency cannot be estimated from available data

Adverse effects of HQ in both adults and children at an average dose of 400 mg PO BID on day 1 and 200 mg PO daily for 4 days may include the following:

- Very common = abdominal pain, nausea, anorexia
- Common = diarrhea, vomiting, headache, skin rash, pruritus, mood changes/emotional lability
- Not known = hypoglycemia (from its sulfonylurea-like effect), prolonged QT interval (from cardiac potassium channel blockade), torsades de pointes (Sanofi-Aventis Canada Inc., 2019)

Other adverse effects such as cardiomyopathy and retinal toxicity would only be expected with chronic use over several weeks, and more likely months or years.

Acute adverse cardiac effects of hydroxychloroquine are well known. It can result in QT prolongation in a dose dependent manner (Roden 2016). Risk factors for further drug-induced QT prolongation include: female gender, advanced heart disease, electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia), hyperthyroidism, family history of congenital long QT syndrome or sudden cardiac death, or co-administration with other QT prolonging medications (included, but not limited to, azithromycin).

In addition to the Alberta clinical trial noted above, there is a clinical trial in France which is planning to study adverse effects of all COVID-19 drug therapies, including CQ. [https://clinicaltrials.gov/ct2/show/NCT04314817?cond=Coronavirus&cntry=FR&draw=2&rank=2](https://clinicaltrials.gov/ct2/show/NCT04314817?cond=Coronavirus&cntry=FR&draw=2&rank=2)

2. Drug Interactions

Drug interactions with HQ are also a concern, especially with other drugs that prolong the QT interval. A patient with a QTc interval > 500 ms is at greater risk for development of torsades des pointes tachycardia (Juurlink, 2020). Patients who are already on QTc prolonging agents and then started on this drug would either require more frequent monitoring of their ECG or a switch to a different drug to prevent QTc prolongation.

HQ is also a substrate of CYP 2C8 and CYP 3A4. 3A4 is the P450 enzyme responsible for metabolizing around 60% of all drugs. Interactions with other substrates (e.g. clarithromycin, PPIs, HMG CoA reductase inhibitors), inducers (e.g. rifampin) or inhibitors (e.g. protease inhibitors, diltiazem) of 3A4 may lead to increased risk of toxicity or decreased effect of HQ.

3. Unintentional pediatric exposure to CQ/HQ in the home
One of the most concerning aspects of CQ is its toxicity in children with unintentional ingestions of someone else’s medication. Ingestion of as little as 1-2 grams can be fatal to small children (ToxiNZ 2020, Cann 1961, Kelly 1990).

Pediatric patients with CQ or HQ toxicity may present with severe manifestations of the adverse effects listed above. This includes seizures, coma, hypoglycemia and dysrhythmias. Since hospitalized patients have their medications administered to them and are stored away from children, unintentional pediatric access is much less of an issue. If used for prophylaxis, it must be anticipated that there will be up to 5 days’ worth of HQ pills in homes with children in them.

A toxic dose for both adult and pediatric patients has not been established. Having said that, a pediatric dose of HQ for malaria treatment is 25 mg/kg over 3 days. Hence, a 2 year old weighing 14 kg would require a total of 350 mg over 3 days.

Using the prophylactic doses above, and assuming the ingestion occurred all at once, there may be anywhere from 1600-3200 mg in the house, for an estimate of 114-228 mg/kg in the same 2 year old.

*How stable is the supply of HQ to Alberta?*

**Chloroquine**

Chloroquine is currently on long term back order, therefore there is no anticipated availability in Alberta at this time.

**Hydroxychloroquine**

Within Alberta Health Services, all current supply of hydroxychloroquine is restricted to patients admitted with COVID-19, as outlined in the [Recommendations for Antimicrobial Management of Adult Hospitalized Patients with COVID-19](https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-recommendations.pdf) (AHS, 2020).

At this time, AHS is confident that there is adequate supply to continue to treat all patients previously on hydroxychloroquine as well as 4,300 patients that would be admitted to an AHS or Covenant facility with COVID-19, assuming treatment of 14 tablets per patient. The current projections for admitted patients is slightly above 2000 patients. AHS continues to work to obtain additional supply of hydroxychloroquine to manage our patient’s needs. Additional sources being looked into include, but are not limited to:

1) Securing additional supply from our current supplier

2) Securing supply announced by Jamp Pharmaceuticals on March 23rd. How supplied is to be divided between the different health authorities has not yet been confirmed

At this time, all hydroxychloroquine prescribing needs to be restricted to hospitalized patients with COVID-19, in accordance with the Recommendations for Antimicrobial Management of Adult Hospitalized Patients with COVID-19. Use for treatment for non-hospitalized patients or prophylaxis for patients/health care providers is not permitted at this time.
In the community, there is limited supply of hydroxychloroquine. The Canadian Pharmacists Association has issued a statement recommending against using hydroxychloroquine in ambulatory patients (Canadian Pharmacists Association, 2020), as has the College of Physicians and Surgeons of Alberta (CPSA, 2020).
Reference List


Hinton D. Re: Request for Emergency Use Authorization for Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied from the Strategic National Stockpile for Treatment of


Additional Resources
1. LexiComp database
2. Micromedex database
3. ToxiNZ Poison Information database
5. Elsevier Novel Coronavirus Information Center.