COVID-19 Scientific Advisory Group Rapid Response Report

Key Research Question: What is the evidence for and risks of using hydroxychloroquine (HQ) as a treatment and prophylaxis for SARS-CoV-2

Context

- There is widespread concern of contracting COVID-19 in both the public and among staff.
- HQ has been suggested as treatment and prophylaxis for COVID-19 illness in social media and in news reports, based on announcements in part from politicians, and some scientific data.
- 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).

Key Messages from the Evidence Summary

- The evidence of HQ effectiveness in treating COVID-19 illness is limited at best. There is plausible activity of HQ against COVID-19 from *in vitro* and *in vivo* data and recent physician experience from China.
- There is minimal evidence for HQ in use as prophylaxis for COVID-19 illness. There are multiple trials underway to explore this, including determining what groups would be considered at highest risk and therefore in need of prophylaxis.
- HQ risks include serious clinical and laboratory adverse effects, potential drug interactions, and pediatric morbidity and mortality.

Recommendations

1. Hydroxychloroquine is not currently recommended to be used as prophylaxis for COVID-19 outside clinical trials, given the lack of established benefit (with no existing data on prophylaxis) to counterbalance potential harms.
2. As there are limited supplies of hydroxychloroquine within AHS pharmacy, 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 good evidence of efficacy, AND, pending more data, for possible use in COVID-19 positive hospitalized patients where the potential benefits outweigh the risks and no clinical trials of COVID-19 therapy are available.
3. For patients with COVID-19 disease in the community, preference is given to enrollment in clinical trials investigating the effects of hydroxychloroquine in preventing severe COVID-19 illness.

Summary of Evidence

Literature for this review was gathered in a targeted strategy, pulling from a pragmatic search of the COVID-19 literature, as well as through medication safety sources (eg: Lexicomp). This is

an important limitation of this review, as there may be evidence from the SARS and MERS experience that was missed by this strategy.

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

Both chloroquine (CQ) and HQ have been shown *in vitro* to inhibit the growth of coronavirus (Keyaerts et al., 2004; 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. *In vivo* studies in mice have also shown that CQ improves survivability in mice infected with human coronavirus (Keyaerts et al., 2009).

In the Chinese experience with COVID-19, CQ was recommended as part of the treatment for established COVID-19 pulmonary disease (Dong et al., 2020, Gao et al., 2020; Liang et al., 2020). Notably, these recommendations were made based on physician experience rather than on clinical trial evidence.

Clinical data includes 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., 2020). 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.

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

As of March 24, 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 prophylaxis of SARS-CoV-2 infection (Clinicaltrials.gov, 2020). A document circulating on Twitter indicates that HQ has been used for COVID-19 prophylaxis in India, using its benefits as a treatment as the rationale for prophylactic treatment (Bargahva, 2020).

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 HCQ prophylaxis for SARS-CoV-2 include the following:

1. Acute adverse effects may include serious clinical and laboratory features.
2. Multiple potential drug interactions with patient's therapeutic medications.
3. Risk of pediatric morbidity and mortality with unintentional exposures.

The first 2 risks have been mitigated in the AHS antimicrobial document by requiring an Infectious Disease consultation prior to starting any COVID-19 antimicrobial therapy, recommending labs and ECG prior to starting therapy, and consultation with a pharmacist or referring to the University of Liverpool website http://www.covid19-druginteractions.org/.

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 access for patients on HCQ for other

conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis) have continued access to therapy. 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 that require therapy the most.

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 CQ. This review will require updating as preliminary data from these trials is made available.

Date question received by advisory group: 24 March 2020

Date report submitted to committee: 26 March 2020

Date of first assessment: 25 March 2020

Date of re-assessment: n/a

COVID-19 Scientific Advisory Group Rapid Response Report

Appendix

List of non-clinical abbreviations

HCQ: Hydroxychloroquine

AHS: Alberta Health Services

CQ: Chloroquine

RCT: randomized controlled trial

CIOMS: Council for International Organizations of Medical Sciences

Evidence Review

Literature for this review was gathered in a targeted strategy, 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 evidence from the SARS and MERS experience that was missed by this strategy.

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

Findings from previous *in vitro* studies have suggested that chloroquine and hydroxychloroquine may inhibit the coronavirus through a series of steps. The drugs can change the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane. It can also inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, virus release and other processes to achieve its antiviral effects.

There are two *in vitro* studies are already referenced within the AHS COVID-19 antimicrobial recommendations document (Yao et al, Wang et al).

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.

There is also one animal study from Belgium that demonstrated that CQ improved survival in mice infected with human coronavirus OC43 (Keyaerts et al). A separate Belgian study demonstrated that CQ demonstrated both antiviral and cytostatic activity in SARS-CoV-cultured cells (Keyaerts et al), which was also demonstrated in a study from the United States (Vincent et al). 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).

Recently, 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. 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., 2020). 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.

A randomized trial comparing hydroxychloroquine and placebo in outpatients with acute COVID-19 illness will be starting in early April 2020.

What is the evidence that HCQ is effective as a prophylactic for COVID-19?
As of March 24, 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 (HCQ) for prophylaxis of SARS-CoV-2 infection.

There are four clinical trials registered on clinicaltrials.gov (2 US, 1 Mexico, and 1 UK) whose purpose is to study the effectiveness of CQ or HCQ prophylaxis in healthcare workers or household contacts of people known to be COVID-19 positive. The start dates for these studies are between March and May 2020, and the end dates for these are between March 2021 and May 2022.

https://clinicaltrials.gov/ct2/show/NCT04303507?term=chloroquine&cond=Coronavirus&draw=2&rank=2

https://clinicaltrials.gov/ct2/show/NCT04318444?term=hydroxychloroquine&cond=Coronavirus&draw=2&rank=1

https://clinicaltrials.gov/ct2/show/NCT04308668?term=hydroxychloroquine&cond=Coronavirus&draw=2&rank=5

https://clinicaltrials.gov/ct2/show/NCT04318015?term=hydroxychloroquine&cond=Coronavirus&draw=2&rank=7

There is a document circulating on Twitter that indicates that the country of India has approved HQ prophylaxis for healthcare workers and household contacts in that country. 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.

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

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)

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.

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

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. 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 HCQ.

3. Unintentional pediatric exposure to HQ in the home

One of the most concerning aspects of HQ 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.

Pediatric patients 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 adults 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.

At this time, AHS is confident that there is adequate supply to continue to treat all patients previously on hydroxychloroquine as well as 2000 patients that would be admitted to an AHS or Covenant facility with COVID-19. The current projections for admitted patients is slightly above 2000 patients, therefore 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 23. 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:https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/CQ-HCQ-COVID-FINAL-EN.pdf. AHS is not able to estimate current HQ stocks within community pharmacies.

Reference List

Alberta College of Pharmacy. (2020). Prescribing of drugs to treat COVID-19 for the purposes of stockpiling. Retrieved from: https://abpharmacy.ca/covid-19-guidance-pharmacists-and-pharmacy-technicians. Accessed 26 March 2020.

Barghava, B. (2020). Advisory on the use of hydroxyl-chloroquinone as prophylaxis for SARS-CoV-2 infection. Indian Council of Medical Research. New Delhi: India.

Clinicaltrials.gov. (2020). Search terms: hydroxychloroquine and coronavirus.

Dong, L., Hu, S., & Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug discoveries & therapeutics*, *14*(1), 58–60. https://doi.org/10.5582/ddt.2020.01012

Gao, J., Tian, Z., & Yang, X. (2020). Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends*, *14*(1), 72–73. https://doi.org/10.5582/bst.2020.01047

Gautret, P., Lagier, J. C., Parola, P., Meddeb, L., Mailhe, M., Doudier, B., ... & Honoré, S. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*, 105949. Retrieved from: https://www.medrxiv.org/content/medrxiv/early/2020/03/20/2020.03.16.20037135.full.pdf. Accessed 26 March 2020.

Keyaerts, E., Vijgen, L., Maes, P., Neyts, J., & Van Ranst, M. (2004). In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochemical and biophysical research communications*, *323*(1), 264–268. https://doi.org/10.1016/j.bbrc.2004.08.085

Keyaerts, E., Li, S., Vijgen, L., Rysman, E., Verbeeck, J., Van Ranst, M., & Maes, P. (2009). Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. *Antimicrobial agents and chemotherapy*, *53*(8), 3416–3421. https://doi.org/10.1128/AAC.01509-08

Kono, M., Tatsumi, K., Imai, A. M., Saito, K., Kuriyama, T., & Shirasawa, H. (2008). Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: involvement of p38 MAPK and ERK. *Antiviral research*, *77*(2), 150–152. https://doi.org/10.1016/j.antiviral.2007.10.011

Liang, T. (2020). Handbook of COVID-19 Prevention and Treatment. Zhejiang University School of Medicine, China. Retrieved from: https://iau-aiu.net/Zhejiang-University-Handbook-of-COVID-19-Prevention-and-Treatment. Accessed: 26 March 2020.

Vincent, M. J., Bergeron, E., Benjannet, S., Erickson, B. R., Rollin, P. E., Ksiazek, T. G., Seidah, N. G., & Nichol, S. T. (2005). Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology journal*, *2*, 69. https://doi.org/10.1186/1743-422X-2-69

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research*, *30*(3), 269–271. https://doi.org/10.1038/s41422-020-0282-0

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E., Song, C., Zhan, S., Lu, R., Li, H., Tan, W., & Liu, D. (2020). In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciaa237. Advance online publication. https://doi.org/10.1093/cid/ciaa237

Additional Resources

1. LexiComp database
2. Micromedex database
3. ToxiNZ Poison Information database
4. Antimalarials. In Goldfrank's Toxicologic Emergencies, 11th ed 2019.
5. Elsevier Novel Coronavirus Information Center. https://www.elsevier.com/connect/coronavirus-information-center?dgcid=_SD_banner#research Accessed March 25, 2020.
6. Hydroxychloroquine product monograph. http://products.sanofi.ca/en/plaquenil.pdf. Accessed March 25, 2020.