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Guidance for OFF LABEL use of Hydroxychloroquine (HCQ) and Chloroquine (CQ) for COVID-19 infected patients

I. PURPOSE, DEVELOPMENT AND GUIDING PRINCIPLES

a) Purpose: The purpose of this document is to provide pharmacologic treatment guidance for clinicians at UN health care facilities who are managing the care of patients diagnosed with coronavirus disease 2019 (COVID-19) and who elect to administer HCQ or CQ to these patients at locations where such treatment is authorized by local health authorities. The guidance provided is based on current knowledge, experience, and expert opinion. The goal is to establish and promulgate a standard approach to the pharmacologic treatment of patients diagnosed with COVID-19. This guidance is not intended to replace or supersede individualized clinical evaluation and management of patients according to clinician’s best judgement based on unique patient factors.

This guidance does not imply an obligation on the part of the physician to participate in this protocol if he/she chooses not to.


c) Guiding principles:
• Guidance is based on expert opinion: At the time of this writing, there is minimal available evidence from randomized clinical trials (RCTs) to support recommendations for the use of any specific pharmacologic treatment for patients with COVID-19. Existing data are mostly drawn from in vitro and nonrandomized studies or are extrapolated from animal models of related coronaviruses.
• Agreed upon definition of patients at high risk based on literature review
• This guidance applies to the treatment of patients under the direct care and monitoring of a physician. Both inpatients and outpatients are eligible under this protocol.
• Infectious diseases consultation for specific higher-risk patients is advised

II. DEFINITION: PATIENTS AT HIGH RISK FOR POOR OUTCOMES

Eligibility:
• Patients suspected or confirmed to have COVID-19 disease (testing for COVID-19 (PCR) is not required but recommended if obtainable on site) and who are at high risk for
poor outcomes, including ARDS and death. These would include individuals age >60, underlying co-morbidities e.g. diabetes, cardiovascular and chronic lung disease, cancer and immunocompromised individuals.

- Conditions covered under the above definition included (but are not limited to):
  - Cardiovascular disease, excluding hypertension as the sole cardiovascular diagnosis
  - Diabetes with A1c level >7.5%
  - Chronic pulmonary diseases, including asthma
  - End-stage renal disease
  - Advanced liver disease
  - Blood disorders (e.g., sickle cell disease)
  - Neurologic or neurodevelopmental disorders
  - Post–solid organ transplantation, on immunosuppressive therapy
  - Use of biologic agents for immunosuppression
  - Undergoing treatment with chemotherapy or immunotherapies for malignancy
  - Within 1-year post–marrow transplant
  - Undergoing treatment for graft-versus-host disease
  - HIV infection, with CD4 cell count <200 copies/mm3

- Any 1 of the following clinical findings:
  - Oxygen saturation (SaO2) <94% on room air; <90% if known chronic hypoxic conditions or receiving chronic supplemental oxygen
  - Respiratory rate >24 breaths/min

- Laboratory finding: D-dimer level >1 μg/mL in patients with respiratory illness
- Any inpatient who, while hospitalized, develops any 1 of the medical conditions or clinical findings listed above.

III. USE OF HCQ or CQ FOR TREATMENT of COVID-19 in PATIENTS at HIGH RISK for POOR OUTCOMES

Note: As of this writing, there are currently no definitive data available on the effectiveness or comparative effectiveness of either HCQ or CQ for the treatment of COVID-19.

- Prescribing clinicians and patients should be aware that drug efficacy for COVID-19 is unclear.
- HCQ is preferred because of better tolerability and lower toxicity. (9)

1 Numbers in brackets refer to the provided references at the end of this document from page 8 onwards.
• Currently, CQ is in shortage and unavailable for ordering.

The guidance in this document is based on very limited evidence that treatment with HCQ or CQ may result in a more rapid reduction in viral shedding and may be associated with improved clinical outcomes (see evidence discussion below).

If HCQ and CQ do have clinically significant antiviral activities, then based on experience with other acute viral infections, it is likely that they will be more effective if initiated as soon as possible. (10)

A. GUIDANCE FOR THE USE OF HCQ or CQ FOR TREATMENT OF COVID-19

Candidates for treatment

• If a clinical trial exists at the treatment location, regarding the use of HCQ or CQ in the treatment of COVID19, enrollment is strongly recommended rather than prescribing either drug.
• Clinicians should evaluate patients with moderate to severe signs of COVID-19 to identify those who are at high risk of poor outcomes. Before prescribing HCQ or CQ (should it become available), Clinicians should weigh the risks and potential benefits (based on low-quality evidence). Candidates for treatment include patients who meet the criteria noted in para II (see above)

• Clinicians should not prescribe HCQ or CQ treatment for any patient who
  o -Does not meet the above criteria for being at high risk of poor outcomes.
  o -Has multiorgan failure. This is due to cardiac concerns with severe COVID-19 and HCQ or CQ use. (11)
  o -Has a QTc >500 ms at baseline, documented cardiomyopathy, or myocarditis. (12)
  o -If HCQ or CQ treatment is initiated in a patient with elevated QTc at baseline (>450 ms in men; >470 ms in women), clinicians should obtain a follow-up electrocardiogram daily for the first 48 to 72 hours.
  o -If QTc increases to >500 ms, clinicians should discontinue HCQ or CQ treatment.

• Clinicians should not delay initiation of HCQ or CQ treatment to obtain either glucose-6-phosphate dehydrogenase (G6PD) status or retinal examination. (13)
• Screening for G6PD deficiency or retinopathy in the context of short-term use of HCQ or CQ for COVID-19 treatment is not recommended.
• Retinal injury has been associated with long-term HCQ or CQ therapy; the American Academy of Ophthalmology does not recommend retinal screening before short-term use. \(^{(14)}\)

**HCQ Treatment Duration and Dosing**

• If a clinician decides to prescribe HCQ after careful assessment of known risks and low-quality evidence of benefit, the dosing scheme below should be used for a 5-day treatment duration. There is no evidence to suggest that treatment beyond 5 days is beneficial.
  
  o -HCQ Day 1 (loading dose): 400 mg by mouth every 12 hours x 2 doses.
  o -Days 2 through 5: 400 mg by mouth every 24 hours.
    With Renal or liver impairment: No dosage adjustment necessary.
  o -In case of gastrointestinal intolerance, HCQ can be dosed at 200 mg by mouth every 12 hours on days 2 through 5.
  o -HCQ tablets can be crushed for administration through a nasogastric (NG) tube.

**CQ Treatment Duration and Dosing (currently unavailable)**

• If a clinician decides to prescribe CQ after careful assessment of known risks and low-quality evidence of benefit, the dosing scheme below should be used for a 5-day treatment duration. There is no evidence to suggest that treatment beyond 5 days is beneficial.
  
  o -CQ 500 mg by mouth every 12 hours.
  o -No loading dose should be administered.
  o -Renal or liver impairment: No dosage adjustment necessary.
  o -CQ tablets can be crushed for administration through an NG tube.

**Combination Therapy**

• Clinicians should not prescribe HCQ and azithromycin combination therapy solely for COVID-19.

• A small, nonrandomized observational study of 36 hospitalized patients with COVID-19 compared 14 patients who were prescribed HCQ alone, 6 patients prescribed HCQ plus azithromycin, and 16 patients prescribed neither agent. HCQ plus azithromycin appeared to lead to faster reduction in viral carriage; however, no pair-wise statistical comparisons were presented, and HCQ failures were removed from analysis. \(^{(15)}\) Whether this observation was spurious or has clinical importance is not known. Combination therapy has the known risk of additive QT increase without benefit.

**Drug interactions (53,54)**
Digoxin: Concomitant hydroxychloroquine sulfate and digoxin therapy may result in increased serum digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.

Antacids and kaolin: Antacids and kaolin can reduce absorption of hydroxychloroquine sulfate; an interval of at least 4 hours between intake of these agents and hydroxychloroquine sulfate should be observed.

Cimetidine: Cimetidine can inhibit the metabolism of hydroxychloroquine sulfate, increasing its plasma level. Concomitant use of cimetidine should be avoided.

Insulin and other antidiabetic drugs: As hydroxychloroquine sulfate may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or other antidiabetic drugs may be required.

Arrhythmogenic drugs: There may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine sulfate is used concomitantly with other arrhythmogenic drugs, such as amiodarone, azithromycin or moxifloxacin.

Ampicillin: In a study of healthy volunteers, hydroxychloroquine sulfate significantly reduced the bioavailability of ampicillin. An interval of at least two hours between intake of ampicillin and hydroxychloroquine sulfate should be observed.

Cyclosporine: After introduction of hydroxychloroquine sulfate, a sudden increase in serum cyclosporine level has been reported. Therefore, close monitoring of serum cyclosporine level is recommended and, if necessary, hydroxychloroquine sulfate should be discontinued.

Mefloquine: Co-administration of hydroxychloroquine sulfate and mefloquine may increase the risk of convulsions.

Praziquantel: In a single-dose interaction study, hydroxychloroquine sulfate has been reported to reduce the bioavailability of praziquantel.

Tamoxifen: Concomitant use of hydroxychloroquine sulfate with drugs known to induce retinal toxicity such as tamoxifen is not recommended.

Antiepileptics: The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine sulfate.

Usage in Pregnancy (53,54)

• In animal studies, embryo-fetal developmental toxicity was shown at doses approximately 3 to 16 times the maximum recommended therapeutic dose based on a body surface area comparison. Preclinical data showed a potential risk of
genotoxicity in some test systems. In humans, at recommended doses for prophylaxis and treatment of malaria, observational studies as well as a meta-analysis, including a small number of prospective studies with hydroxychloroquine sulfate exposure during pregnancy, have shown no increase in the rate of birth defects or spontaneous abortions.

- The individual benefit-risk balance should be reviewed before prescribing hydroxychloroquine sulfate in pregnant women.

**Review of Limited Evidence Regarding Use of HCQ and CQ**

- Currently, there are no agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of COVID-19, and there are no agents with RCT-demonstrated efficacy for the treatment of COVID-19. This document provides guidance for the off-label use of HCQ and CQ (should it become available) based on results from in vitro studies, nonrandomized comparative studies, and a case report series; use in France (16) and Italy (15); and extrapolation from experience treating other diseases.

- HCQ and CQ: HCQ and CQ have been found to have in vitro activity against SARS-CoV-2 and some other viruses. (12,17) However, in vitro activity of these drugs has not translated into effective activity for any viral infection. Notable studies include failure in animal models for Ebola virus or in humans for influenza and HIV. (12,18,19)

- A nonrandomized comparison study from France that included 36 patients described a shorter duration of SARS-CoV-2 viral shedding among the 20 patients who received HCQ and retention of virus in the 16 patients who did not receive HCQ. (16) On day 6 of the study, 70% of the HCQ group compared with 12.5% of the control group had clearance of viral carriage. (16) Results of a post hoc analysis of viral carriage by azithromycin among the 6 patients who received HCQ plus azithromycin are not adequate for guidance on co-administration of azithromycin with HCQ because of the small sample size, lack of statistical significance with a pair-wise comparison, and exclusion of patients whose therapy failed (i.e., death or admission to intensive care). *This study has notable limitations: nonrandomized design, a small number of patients (36), no clinical outcomes, and no correlation between viral carriage and clinical outcomes.*

**HCQ and CQ toxicities:**

- The overall risks associated with HCQ and CQ use are likely low but are unknown in treatment of COVID-19. (9) Prolonged QT and potential arrhythmias are the risks of most concern for critically ill patients. These are of most significant concern in patients with cardiomyopathy. In a case series of 21 critically ill patients with COVID-19 in Washington State, 7 (33%) developed cardiomyopathy. (11) Given the concern for HCQ- or CQ-associated cardiotoxicity in critically ill patients, the risk
associated with use in these patients may outweigh the benefit at later stages of this viral illness. (12) An additional risk is hypoglycemia, as described in multiple case reports. (21-25)

- For patients at high risk for poor outcomes who have not developed cardiac complications, the potential benefit likely outweighs the risk. For patients with mild COVID-19 (i.e., outpatients), the potential risk of treatment with HCQ or CQ outweighs the likely minimal benefit. Similarly, exposing low-risk hospitalized patients to unproven therapy is not recommended.
- Long-term use of HCQ may be associated with retinal toxicities. Short-term use is not associated with retinal damage and may be used in people with preexisting retinal disease, such as diabetic retinopathy or macular degeneration.

The following common and transient adverse effects of HCQ have been reported in ≤1% of patients; gastrointestinal adverse effects are more common with CQ26-29:

- Rash (including pustulosis), pruritus
- Headache, dizziness, tinnitus
- Nausea, vomiting, abdominal pain
- Dry mouth

HCQ and HQ are safe for use in pregnancy (Class B). (30,31)

**B. NO EVIDENCE TO SUPPORT USE OF HCQ FOR PRE-POST EXPOSURE PROPHYLAXIS**

Guidance: Do Not Use HCQ for Pre- or Post-Exposure Prophylaxis

- Clinicians should not prescribe HCQ for pre-exposure prophylaxis or for post-exposure prophylaxis in individuals with confirmed or suspected exposure to SARS-CoV-2.
- There is no experience to support the use of HCQ as pre- or post-exposure prophylaxis. Healthcare workers who have been exposed to SARS-CoV-2 may be eligible for a post-exposure prophylaxis study.
IV. REFERENCES


53. https://www.fda.gov/media/136537/download

54. https://www.fda.gov/media/136536/download