JHMI Clinical Guidance for Available Pharmacologic Therapies for COVID-19

Updated March 25, 2020*; Writing Group of the Johns Hopkins University and Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

Contents

I. Purpose, Development, and Guiding Principles

Purpose: The purpose of this document is to provide pharmacologic treatment guidance for clinicians at Johns Hopkins Hospital (JHH) who are managing the care of patients diagnosed with coronavirus disease 2019 (COVID-19). 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 JHH inpatients diagnosed with COVID-19. This guidance is not intended to replace or supersede individualized clinical evaluation and management of patients according to clinicians' best judgment based on unique patient factors.

Development process: Paul Auwaerter, MD, Clinical Director of Johns Hopkins Medicine Division of Infectious Diseases, convened a working group of Johns Hopkins clinical experts in infectious diseases, pulmonary and critical care medicine, clinical pharmacology, and pharmacy to review and weigh the available evidence regarding treatment of COVID-19.

From the larger working group, a smaller writing group was convened to develop guidance. The group met by conference call twice to define the scope of the guidance, review the evidence, review draft documents, and establish consensus.

* The March 25, 2020, version updates and replaces the version released on March 22, 2020.

COVID-19 Treatment Guidance Writing Group

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- **Consensus guidance:** Following teleconferences and review, writing group suggestions were incorporated into the draft document and all members submitted a vote. The guidance was unanimously approved on March 22, 2020.

  Following additional review and discussion by the writing group and by the full working group, the guidance was updated on March 25, 2020. Key updates are highlighted throughout.

- **Ongoing updates:** New information and experience are reviewed daily, and guidance will be updated as needed. The Johns Hopkins Health System community should feel free to provide comments to: C19workgroup@jhu.edu.

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. To date, the only published RCT results are from a study of lopinavir/ritonavir (LPV/RTV) that found no evidence of benefit in patients with COVID-19.
  - The writing group considered the evidence and potential benefits of the following putative antiviral agents: hydroxychloroquine sulfate (HCQ) or chloroquine phosphate (CQ), remdesivir,[a]

Guiding Principles

LPV/RTV, azithromycin, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs).

- The writing group will consider evidence and potential benefits of the following putative immunosuppressant disease-modifying agents: steroids, tocilizumab, and interferon beta-B1.

- **Agreed upon definition of patients at high risk:** The writing group agreed on described or likely risk factors for individuals at high risk of poor outcomes (i.e., need for intensive care, acute respiratory distress syndrome [ARDS], or death); see Section II.
- **This guidance applies to the treatment of inpatients only:** At the time of this draft, the writing group does *not* support the outpatient treatment of patients with COVID-19 using the agents discussed below.
- **Rapid response to emerging evidence and experience:** Recognizing that knowledge of and experience with COVID-19 is evolving rapidly, the writing group is committed to updating guidance regularly as new evidence or experience is available.
- **Infectious diseases consultation for specific higher-risk patients is advised:** The writing group recommends that prescribing clinicians consult with infectious diseases clinicians for treatment of any recipient of or candidate for solid organ or bone marrow transplant. Consultation with infectious diseases clinicians for evaluation or management of any hospitalized person with suspected (person under investigation [PUI]) or confirmed COVID-19 is otherwise up to the judgment and needs of the primary team.

[a.] For remdesivir, information about an available clinical trial is provided in Section V. Currently, remdesivir appears promising based on data from in vitro and animal models. Therefore, entry into the remdesivir RCT is preferred if a patient agrees and meets the entry criteria.

II. Definition: Patients at High Risk for Poor Outcomes

Patients diagnosed with COVID-19 who are at high risk for poor outcomes, including ARDS and death, are those who meet any 1 of the following criteria:

- Age ≥65 years
- Any 1 of the following medical conditions:
  - 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/mm^3

- 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.

Evidence: This definition of patients at high risk for poor outcomes has been established based on an analysis of factors associated with in-hospital death among patients with COVID-19 in China and conditions associated with increased disease severity among patients with seasonal influenza.[1-3] Specifically, older age, decreased oxygen saturation, and D-dimer level >1 µg/mL were associated with COVID-19–related mortality in China.[4,5]

Many of the underlying conditions listed were not present in sufficient numbers for evaluation in published studies on COVID-19. The following conditions, known to predispose patients to more severe or prolonged influenza, also have been included: diabetes, heart failure, end-stage kidney disease, advanced HIV, and use of immunosuppressive agents.[1-3] Future studies are likely to refine the risk stratification. Whether pregnant patients are at higher risk for severe COVID-19 infection is not known.

III. Use of Antiviral and Immunomodulatory Agents

Available data are limited, and there are minimal RCT data on the effectiveness of antiviral or immunomodulatory agents for the treatment of COVID-19. The only reported RCT of available drugs is an open-label study of LPV/RTV from China, in which treatment with LPV/RTV was *not* found to improve clinical outcomes among hospitalized patients.[6]

Given the dearth of high-quality evidence, this writing group has formulated the guidance in this document based on limited data (data available as of 3-25-2020) and expert opinion. Currently, guidance is limited to the use of HCQ or CQ.

Remdesivir is an antiviral agent with activity against Ebola virus in humans and other coronaviruses in nonhuman primates.[7,8] There is an active randomized placebo-controlled clinical trial enrolling at JHH; see Section V for information.

IV. Use of HCQ or CQ for Treatment of COVID-19 in Patients at High Risk for Poor Outcomes

Note: As of this writing (3-25-2020), 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]
- 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]

Guidance for the Use of HCQ or CQ for Treatment of COVID-19

Candidates for Treatment

- If a clinical trial exists regarding the use of HCQ or CQ, enrollment is strongly recommended rather than prescribing either drug.
- Clinicians should evaluate patients admitted for inpatient management 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 any 1 of the following criteria:
  - Age ≥65 years
  - Any 1 of the following medical conditions:
    - Cardiovascular disease, excluding hypertension as a 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/mm^3
  - Any 1 of the following clinical findings:
    - 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 the setting of respiratory illness
- Any inpatient who, while hospitalized, develops any 1 of the medical conditions or clinical findings listed above.

- **Clinicians should *not* prescribe HCQ or CQ treatment for any patient who:**
  - Does not meet at least 1 of the above criteria for being at high risk of poor outcomes.
  - Is not admitted for inpatient care.
  - Has multiorgan failure. This is due to cardiac concerns with severe COVID-19 and HCQ or CQ use.[11]
  - Has a QTc >500 ms at baseline, documented cardiomyopathy, or myocarditis.[12]
  - 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.
  - If QTc increases to >500 ms, clinicians should discontinue HCQ or CQ treatment.

Guidance for the Use of HCQ or CQ for Treatment of COVID-19

- 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.
  - HCQ Day 1 (loading dose): 400 mg by mouth every 12 hours x 2 doses.
  - Days 2 through 5: 400 mg by mouth every 24 hours.
  - Renal or liver impairment: No dosage adjustment necessary.
  - In case of gastrointestinal intolerance, HCQ can be dosed at 200 mg by mouth every 12 hours on days 2 through 5.
  - 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.
  - CQ 500 mg by mouth every 12 hours.
  - No loading dose should be administered.
  - Renal or liver impairment: No dosage adjustment necessary.
  - 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. Section IV.A includes a detailed critique.

A. 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,[11] 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 CQ[26-29]:

- 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- or 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 (covid19@umn.edu; NCT04308668).

V. Use of Remdesivir

Because JHH is a study site for an RCT with remdesivir, clinicians cannot prescribe this medication for compassionate use while the RCT is enrolling.

Guidance for the Use of Remdesivir for Treatment of COVID-19

- While the Adaptive COVID-19 Treatment trial with remdesivir is ongoing, the lab will notify the study team when a patient is diagnosed with COVID-19; the study team will then assess for study eligibility. The attending physician will be notified if a patient meets eligibility criteria (see below) so study participation[a,b] can be discussed with the patient or the patient's representative.
- Questions can be directed to Katherine Fenstermacher (phone: 804-695 4720, email: kfenste1@jh.edu).
  - **Inclusion criteria**: For enrollment, patients must be ≥18 years old, with COVID-19 confirmed by a laboratory <72 hours prior to randomization (can be a repeat confirmation after an initial diagnosis if >72 hours prior to randomization) and have least 1 of the following:
    - Radiographic infiltrates
    - Clinical assessment of rales/crackles or SaO2 ≤94%
    - Required supplemental oxygen
    - Required mechanical ventilation
  - **Exclusion criteria:**
    - Alanine aminotransferase or aspartate aminotransferase level >5 times upper limit of normal
    - Estimated glomerular filtration rate <50 mL/min or required hemodialysis
    - Pregnant or breastfeeding

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a. Treatment with HCQ, CQ, or any other putative antiviral for COVID-19 must be discontinued before trial participation. Patients taking HCQ chronically for a pre-existing condition may continue the agent if enrolled in the RCT.

b. Patients who participate in the RCT may not be treated for COVID-19 with HCQ or CQ, and they have a 50% chance of receiving a placebo. Remdesivir is expected to be more effective against SARS-CoV-2; therefore, the 50% chance of receiving a more effective treatment makes RCT participation a reasonable choice.

Remdesivir has in vitro activity against SARS-CoV-2 and other coronaviruses.[32,33] Remdesivir has been tested in humans for treatment of Ebola virus infection and performed as well as ZMapp but was inferior to human monoclonal antibodies.[7]

In a mouse model, remdesivir was effective when tested as treatment for SARS-CoV-1,[33] and it was tested in both a mouse and a primate model for MERS-CoV.[8,34] Compassionate use of remdesivir has also been described for SARS-CoV-2.[35]

VI. Use of Other Agents With Speculative or No Established Benefit Against COVID-19

Do Not Use as a Therapeutic Agent for Treatment of COVID-19 Specifically

- Because there is no evidence of efficacy or effectiveness, clinicians should not use any of the following agents for the treatment of COVID-19 in hospitalized patients.
- **Note:** There is no evidence that any of the following agents are harmful in patients with COVID-19 when used to treat other conditions.
  - ACE inhibitors or ARBs (either initiation or discontinuation of use)

- Azithromycin
- Baloxavir marboxil
- Darunavir/ritonavir
- Favipiravir (not FDA-approved or available in the United States)
- Indomethacin or other nonsteroidal anti-inflammatory drugs (NSAIDs)
- Lopinavir/ritonavir
- Nitazoxanide
- Oseltamivir
- Ribavirin
- Umifenovir (not FDA-approved or available in the United States)

For the agents listed above, either there is no plausible evidence of in vitro activity or there is reported in vitro activity but no clinical experience.

ACE inhibitors or ARBs: Host cell entry by SARS-CoV-2 appears to depend on the ACE2 receptor.[36] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor, resulting in no clinical benefit. Chronic use of ACE inhibitors and ARBs upregulate ACE2 expression,[37] as do some chronic conditions, such as diabetes. This has led to concerns of a theoretical risk with use of ACE inhibitors or ARBs. At present, there are no clinical data indicating an increased risk of severe disease among individuals receiving either class of agent, and the time from agent discontinuation to downregulation of ACE2 is likely measured in days.

ACE inhibitor or ARB therapy should not be discontinued because of a COVID-19 diagnosis. Existing clinical recommendations for discontinuation of treatment with ACE inhibitors or ARBs should be followed. There is no evidence to support the use or discontinuation of such agents for the treatment or prevention of COVID-19.

Azithromycin: In a small, prospective case series, the addition of azithromycin to HCQ in 6 patients may have reduced viral carriage, but the results are not adequate to support clinical use of this combination.[16] No efficacy was found in a study of azithromycin against MERS-CoV.[38]

Baloxavir: Baloxavir is licensed for use as a treatment for influenza within 48 hours of symptom onset. The question of its use for treating COVID-19 has been raised; however, as of this writing, the national clinical trials database, clinicaltrials.gov, does not include any studies of baloxavir as an agent against SARS-CoV-2.

Darunavir/ritonavir (DRV/RTV): This combination has weak in vitro activity against SARS-CoV-2.[39] Given the similar mechanism of action of DRV and lopinavir (LPV; see below), it is unlikely that DRV would provide benefit if LPV does not.

Favipiravir: This agent has been used in China to treat patients with COVID-19.[40,41] An open-label, nonrandomized clinical trial comparing favipiravir with LPV/RTV suggested that favipiravir reduced duration of viral shedding and led to more rapid improvement in chest computed tomography (CT) findings.[41] An RCT comparing favipiravir with umifenovir reported a 7-day "clinical recovery rate" of 61% for favipiravir and 52% for umifenovir (P=0.1). A statistically significant reduction in duration of fever was reported for favipiravir.[40] This drug is not approved by the U.S. FDA and is not available in the United States.

Indomethacin or other NSAIDs: Indomethacin (INDO) has been suggested as a possible therapeutic agent, given the hypothesis that prostaglandins have antiviral activity. In vitro studies of INDO against canine corona virus (CCoV) suggested viral inhibition; treatment with INDO reduced viral titers in dogs with CCoV, and INDO reduced growth of SARS-CoV-1 in vitro.[42] These findings are intriguing, but

correlation with clinical outcomes in humans is required before use of INDO can be recommended for treatment of COVID-19.

A March 11, 2020, letter hypothesized a potential worsening of COVID-19 with the use of ibuprofen and has caused concern about the potential risk of ibuprofen if used to treat patients with COVID-19.[43] Similar to ACE inhibitors and ARBs, ibuprofen has been reported to upregulate ACE2 receptors. However, there currently are no published clinical data to suggest an increased risk in patients with COVID-19 using NSAIDs. In general, acetaminophen is preferred for treatment of fever in patients with COVID-19, but therapy should be individualized for hospitalized patients, taking into consideration kidney and liver function.

LPV/RTV: This combination has weak in vitro activity against SARS-CoV-2. Although it was widely used in China, an RCT from China reported no clinical benefit among patients hospitalized with COVID-19 who were given LPV/RTV.[44]

Nitazoxanide: This agent has been tested in vitro against MERS-CoV and found to have activity.[45] There are no animal or human data from studies of use against SARS-CoV-2.

Oseltamivir: Coronaviruses are *not* known to utilize neuraminidase in viral replication; therefore, oseltamivir is not likely to be of any therapeutic value. One case series from China reported that, of 138 hospitalized patients with COVID-19, 124 (89.9%) received oseltamivir, with no reported evidence of benefit.[46]

Umifenovir: This agent was routinely used in China to treat patients with COVID-19.[47] There are no data to support its effectiveness. This drug is not approved by the U.S. FDA and is not available in the United States.

Ribavirin (RBV): In a systematic review, RBV was not found to be beneficial against SARS-CoV-1.[48] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[49]

VII. Use of Immune Modulatory Agents to Treat COVID-19

Guidance for the Use of Immune Modulatory Agents to Treat COVID-19

- Clinicians should *not* prescribe corticosteroids specifically for the treatment of COVID-19.

Corticosteroids: These agents are appropriate for use when indicated for other conditions but should not be prescribed solely for the treatment of COVID-19.

Interferon beta-B1: (to be developed)

Statins: (to be developed)

Tocilizumab: (to be developed)

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