# JHMI Clinical Guidance for Available Pharmacologic Therapies for COVID-19

**Updated April 07, 2020, and replaces the document of March 25, 2020**; Writing Group of the Johns Hopkins University and Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

## Contents

**What's New?** April 7, 2020, Update

- **Criteria for patients with coronavirus disease 2019 (COVID-19) at high risk for poor outcomes have been updated as follows**:
  - Cardiovascular disease, *excluding hypertension as the sole cardiovascular diagnosis* [italicized text is new].
  - Laboratory finding: D-dimer level >1 µg/mL *in patients with respiratory illness* [italicized text is new].
- **Hydroxychloroquine (HCQ) and chloroquine phosphate (CQ):**
  - Added discussion of a new randomized clinical trial (RCT).[1]
  - Updated guidance language:
    - If a Johns Hopkins (JH) clinical trial exists regarding the use of HCQ or CQ, enrollment is strongly recommended rather than prescribing either drug.
    - Before prescribing HCQ (or CQ should CQ become available), clinicians should weigh the risks and theoretical benefits (based on low-quality evidence).
  - **CQ treatment duration:** Changed from 7 days to 5 days, with no loading dose.
  - **HCQ and CQ toxicities:** Hypoglycemia added as a risk.
- **Indomethacin:** Discussion of use added.
- **Lopinavir/ritonavir (LPV/RTV):** Added discussion of additional RCTs[2,3] with mixed findings on viral clearance and time drug was started in the disease course.
- **New section:** *Use of Immune Modulatory Agents to Treat COVID-19*.

# I. Purpose, Development, and Guiding Principles

## A. Purpose

The purpose of this document is to provide pharmacologic treatment guidance for clinicians at Johns Hopkins Hospital (JHH) and the Johns Hopkins Health System who are managing the inpatient 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 **assessing possible 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.

## B. 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 meets regularly by conference call (beginning March 19, 2020), to define the evolving scope of the guidance, review evidence as it becomes available, review draft documents, and ensure consensus.

**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.

## C. COVID-19 Treatment Guidance Writing Group

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## D. Guiding Principles

- **Clinical trial participation is recommended:** The writing group strongly recommends that patients who meet inclusion criteria participate in available clinical trials when they are available.
- **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 (often unpublished) studies, or are extrapolated from animal models of related coronaviruses.

  - The writing group considered the evidence and theoretical benefits of the following putative antiviral agents: hydroxychloroquine sulfate (HCQ) or chloroquine phosphate (CQ), remdesivir, lopinavir/ritonavir (LPV/RTV), azithromycin, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs).
  - The writing group considered the evidence and potential benefits of the following immune acting disease-modifying agents: steroids, tocilizumab and other interleukin-6 (IL-6) pathway agents, and interferon beta-1b.

- **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. The writing group recognizes the controversial nature of providing advice that draws upon minimal data. Opinions do range from only providing drugs within the context of a therapeutic trial to providing drugs with theoretical but possible benefit if risks of adverse reactions are deemed acceptable.
- **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).
- **This guidance applies only to the treatment of inpatients:** At the time of this draft, the writing group does *not* support the outpatient treatment of patients with COVID-19 using HCQ or CQ, or tocilizumab, or any of the agents for which guidance is provided below.
- **Infectious diseases consultation for specific high-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.

# II. Participation in Clinical Trials Is Strongly Recommended

## A. Rationale

Multiple agents have theoretical value in the management of COVID-19 disease; however, actual clinical trial data that establish true efficacy are lacking. Also lacking are clinical trial data to answer the question of optimal timing for the use of theoretically beneficial agents, even as the body of anecdotal evidence of benefits expands rapidly. For these reasons, the writing group favors participation in clinical trials to improve patient access to agents and to increase clinical knowledge.

## B. Currently Available Clinical Trials and Investigational Drug Use

The clinical trials noted below are expected to start enrollment soon or are enrolling patients at the time of this writing. See www.clinicaltrials.gov.

### 1. Remdesivir (active)

The JHH attending physician will be contacted if a patient meets eligibility criteria (see below) so they can discuss study participation with the patient or the patient's representative. Katherine Fenstermacher can be contacted for specific questions (kfenste1@jhu.edu). See the Remdesivir section, below, for more details.

### 2. Convalescent Plasma COVID-19 or Serum-Containing Neutralizing Antibodies (active)

The U.S. Food and Drug Administration (FDA) has authorized an emergency investigational new drug (eIND) application for expanded access to convalescent plasma for patients who meet eligibility criteria (as for any IND use, informed consent is required). The FDA will not provide the convalescent plasma; clinicians must procure it from a blood bank. The JH blood bank does not have COVID-19 convalescent plasma as of this writing. See the *Convalescent Plasma or Serum-Containing Neutralizing Antibodies for Treatment of COVID-19*, below, for more details.

### 3. Hydroxychloroquine

- AIDS Clinical Trial Group (ACTG) 5395, pending: Outpatient HCQ study; Kelly Dooley, MD, MPH, PhD, is the JHH Investigator of Record.
- ACTG 5396, pending: Inpatient HCQ study); David Sullivan, MD, is the JHH Investigator of Record.

# III. Use of Antivirals for Treatment of COVID-19

## A. Hydroxychloroquine (HCQ) and Chloroquine (CQ)

**Rationale for HCQ or CQ:** The guidance in this document is based on very limited evidence that treatment with HCQ or CQ may potentially result in a more rapid reduction in viral shedding (see evidence discussion below). Prescribing clinicians and patients should be aware that medication efficacy for COVID-19 is unclear. 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.[4] HCQ is preferred over CQ because of better tolerability and lower toxicity[5] and because, currently, CQ is in shortage and not available for ordering.

**Guidance 1: Use of HCQ or CQ for Treatment of COVID-19**

**Clinical Trial Participation**

- The writing group strongly recommends that patients participate in available clinical trials when they are eligible and agree to do so. If an active JH clinical trial of HCQ or CQ treatment for COVID-19 is available, enrollment is strongly recommended over prescription of either medication.

**Considerations for Treatment of Patients at High Risk of Poor Outcomes**

- Clinicians should evaluate individuals admitted for inpatient management who have either a laboratory or clinical diagnosis of COVID-19 to identify those who are at high risk of poor outcomes. Note: In patients for whom there is high suspicion for COVID-19 without laboratory confirmation, approval from hospital epidemiology and infection control (HEIC) infectious diseases faculty is required for HCQ (contact Pharmacy for the on-call attending's name).
- Before prescribing HCQ (or CQ should it become available), clinicians should weigh the established risks and theoretical benefits (based on low-quality evidence).
- Clinicians may consider treatment with HCQ (or CQ should it become available) in patients at high risk of poor outcomes, including those 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 disease, including asthma

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        - 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-stem cell transplant or receiving therapy for graft vs. host disease
        - HIV infection, with CD4 cell count <200 copies/$mm^3$
    - Any 1 of the following clinical findings:
        - Arterial 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 the setting of respiratory illness
- Any inpatient who, while hospitalized, develops any 1 of the medical conditions or clinical findings listed above.

**Discharge of Patients on HCQ or CQ Therapy**

- If HCQ (or CQ) treatment is initiated while a patient is hospitalized, clinicians should discontinue therapy if the patient is discharged and has not completed the 5-day treatment course. HCQ or CQ therapy should not be prescribed for outpatient treatment, even if the recommended course of treatment was not completed at the time of discharge. This rationale is based on a lack of evidence suggesting that continued treatment of patients who have improved is necessary, the long half-life of HCQ, and the limited supply of these drugs.

**Patients Who Are Not Eligible for HCQ or CQ Therapy**

- 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.
    - Does not have a laboratory diagnosis of COVID-19 or high suspicion for a clinical diagnosis of COVID-19.
    - Has multiorgan failure (new impairment in pulmonary, kidney, liver, and cardiovascular function). This is due to cardiotoxicity concerns with severe COVID-19 and HCQ or CQ use.[6,7]
    - Has a QTc >500 ms at baseline (or QTc >550 ms in patients with wide QRS >120 ms),[6] documented cardiomyopathy, or myocarditis.[7]
    - 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.
- Clinicians should not delay initiation of HCQ or CQ treatment to obtain either glucose-6-phosphate dehydrogenase (G6PD) status or retinal examination.[8]
    - Screening for G6PD deficiency or retinopathy in the context of short-term use of HCQ or CQ for COVID-19 treatment is not recommended.

**Guidance 1: Use of HCQ or CQ for Treatment of COVID-19**

- 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; use is contraindicated in patients with existing retinal pathology.[9]

**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.
  - 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

    Total duration: 5 days
  - 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.
  - **Do not use azithromycin or fluoroquinolones with HCQ because of additive risk for QTc prolongation.** If atypical coverage is needed for the treatment of community-acquired pneumonia, doxycycline can be used in place of these agents. *See the discussion below*.

**CQ Treatment Duration and Dosing (CQ is 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

    Duration: 5 days
  - 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.
  - **Do not use azithromycin or fluoroquinolones with CQ because of additive risk for QTc prolongation.** If atypical coverage is needed for the treatment of community-acquired pneumonia, doxycycline can be used in place of these agents. *See the discussion below*.

## 1. Patients for Whom HCQ or CQ Treatment May Be Considered

**Patients at high risk of poor outcomes:** The definition of patients at high risk for poor outcomes was developed based on an analysis of factors associated with in-hospital death among patients with COVID-19 in China, preliminary reports from the United States and Europe, and conditions associated with increased disease severity among patients with seasonal influenza.[10-12] Specifically, older age, SaO2, and D-dimer level >1 µg/mL were associated with COVID-19–related mortality in China.[13-15] As more is learned, we expect these definitions will be updated.

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.[10-12] Future studies are likely to refine the risk stratification. Whether pregnant patients are at higher risk for severe COVID-19 infection is not known.

Currently, there are no agents approved by the FDA FDA for the treatment of COVID-19, although the FDA has granted an Emergency Use Authorization for HCQ and CQ.[16] Additionally, there is no high-quality

RCT-demonstrated evidence supporting the use of HCQ or CQ for 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 small RCTs, in vitro studies, nonrandomized comparative studies, and a case report series; use in France[17] and Italy[18]; and extrapolation from experience treating other diseases.

## 2. Review of Limited Evidence Regarding Use of HCQ and CQ

**HCQ and CQ:** HCQ and CQ have been found to have in vitro activity against SARS-CoV-2 and some other viruses.[19,20] 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 and failed trials in humans for influenza and HIV.[21-23]

**Clinical data for COVID-19 (mostly from non-peer reviewed, unpublished reports):**

- **Chen J. [preprint; March 3, 2020][1]:** This small RCT (n = 30) from China compared results in patients randomized to receive HCQ 400 mg daily for 5 days or usual care. Seven days after randomization, 13 of 15 (86%) patients in the HCQ group and 14 of 15 (93%) patients in the control group had negative polymerase chain reaction (PCR) results on pharyngeal swab.
- **Chen Z. [preprint; April 1, 2020][24]:** Another RCT from China in which 62 patients with mild illness were randomized to receive HCQ or usual care. Fever resolved more rapidly in the HCQ group (2.2 days vs. 3.2 days), and there was more radiographic improvement in pneumonia (81% vs. 55%; *P*=.05). This study is limited by the quality of the endpoints, a failure to describe the additional treatment patients were receiving (steroids, antiviral agents, and immunoglobulins), and the known mild antipyretic activity of HCQ, which makes fever an outcome of limited value.
- **Gautret P. [Epub ahead of print; March 20, 2020][17]:** This nonrandomized comparison study from France that included 36 patients described the duration of viral shedding.[17] On day 6 of the study, 70% of the HCQ group compared with 12.5% of the control group had clearance of viral carriage.[17] Results of a post hoc analysis of viral carriage by azithromycin among the 6 patients who received HCQ plus azithromycin indicated clearance in 100%. The lack of pair-wise comparisons and exclusion of patients on HCQ who had progression of disease (i.e., death or admission to intensive care) are two of the many limitations of this study.
- **Gautret P. Preprint[25]:** This follow-up from the original study from France, above, included 80 patients with mild COVID-19 (4 were asymptomatic), all of whom received HCQ plus azithromycin. Only 15% of patients progressed to requiring supplemental oxygen, and 3 were transferred to a medical intensive care unit. Most patients had a negative pharyngeal PCR result for SARS-CoV-2 by day 8. No conclusions can be drawn regarding the effect of HCQ plus azithromycin because there was no comparator arm.
- **Molina J. M. [journal pre-proof; March 28, 2020][26]:** A group in France measured viral clearance among 11 patients treated with HCQ and azithromycin. One patient died and another patient's therapy was stopped because of QT prolongation. Among the surviving patients, 80% had positive nasopharyngeal PCR results for SARS-CoV2 at day 5 or 6 of treatment. This is in contrast to the prior reports from France (Gautret, et al.), above.

**HCQ and CQ toxicities:** The overall risks associated with HCQ and CQ use are likely low but are unknown in treatment of COVID-19.[5] Prolonged QT interval and potential **arrhythmias** are the risks of most concern for critically ill patients. These are the most significant concerns in patients with cardiomyopathy. In a case series of 21 critically ill patients with COVID-19 in Washington State, 7 (33%) developed cardiomyopathy.[27] 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.[7] An additional risk is **hypoglycemia**, as described in multiple case reports.[28-32]

For patients at high risk for poor outcomes who have not developed cardiac complications, the potential benefits may outweigh the risks of treatment; therefore, the decision must be discussed with the patient or the patient's surrogate. Based on currently available data, it may be reasonable to conclude that the

known risks of treatment outweigh the theoretical benefits for a given patient. For patients with mild COVID-19 (i.e., outpatients), the potential risk of treatment with HCQ or CQ likely outweighs the potential 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[33-36]:

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

HCQ and CQ are safe for use in pregnancy (Class B).[37,38]

**No evidence to support the use of HCQ for pre- or post-exposure prophylaxis:** 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).

☑ **Clinicians should *not* prescribe HCQ for pre-exposure prophylaxis or post-exposure prophylaxis in individuals with confirmed or suspected exposure to SARS-CoV-2.**

## B. Remdesivir

**Rationale for use:** Remdesivir is an intravenous (IV) medication that has in vitro activity against SARS-CoV-2 and other coronaviruses.[39,40] 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.[41] In a mouse model, remdesivir was effective when tested as a treatment for SARS-CoV-1,[40] and it was tested in both a mouse and a primate model for MERS-CoV.[42,43] Compassionate use of remdesivir has also been described for SARS-CoV-2.[44]

Because JHH is a study site for an RCT with remdesivir, clinicians cannot prescribe this medication for compassionate use while the RCT is enrolling. Inclusion and exclusion criteria for the clinical trial are as follows:

- **Inclusion criteria**: For study 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

## C. Agents With Speculative Antiviral Effect Against COVID-19

**Guidance 2: Do Not Use These Agents for Treatment of COVID-19 Specifically**

- Because there is no evidence of their efficacy or effectiveness, clinicians should not use any of the following agents for the treatment of COVID-19 specifically 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)
  - Ivermectin
  - Lopinavir/ritonavir
  - Nitazoxanide
  - Oseltamivir
  - Ribavirin
  - Umifenovir (not FDA-approved or available in the United States)
  - Vitamin C
  - Zinc

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

- **ACE inhibitors or ARBs:** Host cell entry by SARS-CoV-2 appears to depend on the ACE2 receptor.[45] 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,[46] 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, no clinical data are 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.[47]
- 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 the clinical use of this combination.[17] No efficacy was found in a study of azithromycin against MERS-CoV.[48]
- **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.[49] 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 inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.[50,51] An open-label, nonrandomized clinical trial comparing favipiravir with LPV/RTV suggested that favipiravir reduced duration of viral shedding and led to a more rapid improvement in chest computed tomography (CT) findings.[51] An RCT comparing favipiravir with umifenovir (brand name Arbidol; a fusion inhibitor approved for use in influenza in Japan and Russia) reported a 7-day "clinical recovery rate" of 61% for favipiravir and 52% for umifenovir (*P*=.1). A statistically significant reduction in duration of fever was reported for favipiravir.[50] This drug is not approved by the 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 coronavirus (CCoV) suggested viral inhibition; treatment with INDO reduced viral titers in dogs with CCoV, and INDO reduced growth of SARS-CoV-1 in vitro.[52] 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.

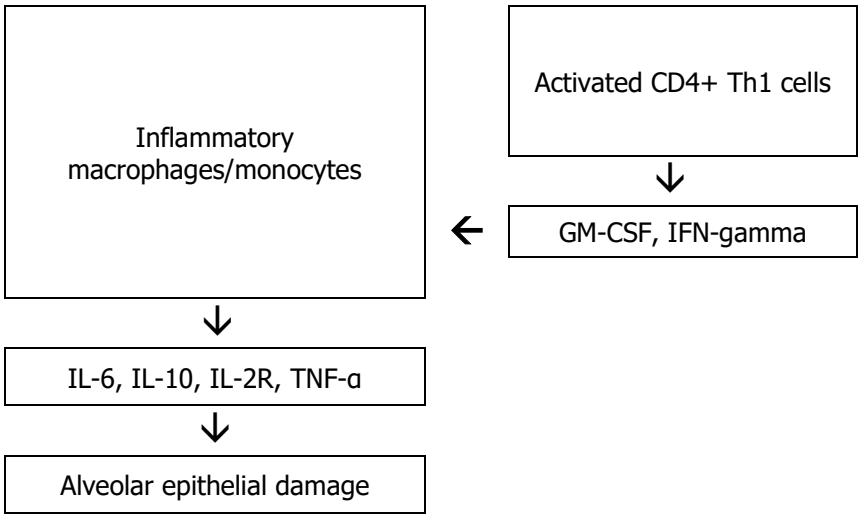
  A March 11, 2020, letter hypothesized a potential worsening of COVID-19 with the use of ibuprofen and has caused concern about the potential risk of ibuprofen if used to treat patients with COVID-19.[53] Similar to ACE inhibitors and ARBs, ibuprofen has been reported to upregulate ACE2 receptors. However, 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.
- **Ivermectin:** There is only in vitro evidence that Ivermectin may inhibit SARS-CoV-2 replication.[54]
- **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; many of the study patients were also receiving other putative antiviral agents.[2] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[3]
- **Nitazoxanide:** This agent has been tested in vitro against MERS-CoV and SARS-CoV-2 and found to have activity.[55] There are no animal or human data from studies of use against SARS-CoV-2.
- **Oseltamivir:** Coronaviruses are *not* known to use 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.[56]
- **Umifenovir:** This agent was routinely used in China to treat patients with COVID-19.[57] There are no data to support its effectiveness. This drug is not approved by the 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.[58] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[59]
- **Vitamin C:** Vitamin C has been suggested as a treatment option for COVID-19. This is based on a prospective randomized trial of IV vitamin C in patients with sepsis and ARDS.[60] In that trial, there was no difference in the primary endpoint of sequential organ failure assessment (SOFA) score between the vitamin C and placebo groups. Differences were not found in several of the 46 secondary endpoints, including 28-day mortality, although these differences were not statistically significant if accounting for multiple comparisons.
- **Zinc:** Zinc lozenges may reduce symptoms of upper respiratory tract infections. There are no clinical data to suggest that zinc benefits patients with COVID-19-associated viral pneumonia.[61]

# V. Use of Immune Modulatory Agents to Treat COVID-19

The natural history of severe COVID-19 appears to be an initial viral pneumonia followed in some patients by a cytokine release syndrome (CRS)-type response. The onset of pneumonia is characterized by fever, cough, fatigue, myalgia, dyspnea, and a radiographic finding of ground-glass opacities in the lungs, along with lymphocytopenia, also commonly observed.[62,63] CRS can occur approximately 5 to 10 days into the disease course (Figure 1). This CRS is characterized by high fevers, rapid worsening of respiratory status, alveolar filling pattern on imaging, elevations in laboratory markers associated with specific inflammatory pathways such as IL-6 and nonspecific markers of inflammation including D-dimer, C-reactive protein (CRP), and ferritin. Patients may progress to multi-organ failure as a result of the CRS or uncontrolled viral infection.[64]

If immune modulatory agents can alter the disease course, they should be considered for use only after a transition to an inflammatory phenotype is identified. Because patients may be hospitalized after experiencing symptoms for a week, this transition may have occurred before or simultaneously with hospitalization.

**Figure 1: Potential Mechanisms of ARDS with SARS-CoV-2[65,66]**




**Abbreviation key:** ARDS, acute respiratory distress syndrome; IL-6, interleukin 6; IL-10, interleukin 10; IL-2R, interleukin-2 receptor; Th1, T helper type 1; TNF-α, tumor necrosis factor-alpha; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-gamma, interferon-gamma

To date, there is no compelling clinical evidence to suggest that immune modulatory therapy is helpful for COVID-19, other than anecdotes, one small case series, and analogies between COVID-19 and other inflammatory conditions. However, given the severity of COVID-19 illness, some clinicians have employed immune modulatory therapies in cases of severe illness. Such decisions require consideration of anticipated risks and theoretical benefits, institutional access processes, and limited supplies.

- ☑ **If available, participation in a clinical trial of immune modulator therapy for COVID-19 is strongly preferred.**

☑ **Patients should be considered for immune modulator therapy for COVID-19 outside of a clinical trial ONLY if: a) no clinical trial is available; b) there is limited access to an available clinical trial; or c) the patient is ineligible for participation.**

## A. Corticosteroids

**Review of the evidence:** An RCT of corticosteroids for bronchiolitis among children found no clinical benefit or notable harm.[67] A meta-analysis of 10 observational studies of corticosteroid use for influenza found that these agents may increase the risk of mortality.[68] Several published observational studies of corticosteroid use in the treatment of SARS-CoV-1 have reported adverse effects and no benefit.[69] A retrospective study from China compared 26 patient who received methylprednisolone with 20 patients who did not; all patients had relatively mild disease. The authors reported no clear benefits or harms associated with methylprednisolone use in the study.[70] Steroids may have a role in managing septic shock or relative adrenal insufficiency and should be used as needed in critical care management.[71] There is anecdotal evidence but no published data on the use of corticosteroids in place of other immune modulator agents in patients who are critically ill with COVID-19 with signs of severe CRS.

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

## B. IL-6R or IL-6 Monoclonal Antibodies

**Choice of agent:** If a clinician considers treatment with a monoclonal antibody (mAb) after weighing the risks and unproven benefits, tocilizumab is the preferred agent because there is some very limited experience with its use in the treatment of COVID-19.[72]

Although published clinical data on and experience with management of CRS associated with either chimeric antigen receptor T-cell therapy (CAR-T) or COVID-19 are limited, siltuximab (an IL-6 inhibitor) may be an alternative if tocilizumab is not available based on the plausibility of similar effects. (As of this writing, sarilumab and anakinra are not available for use in treating COVID-19 throughout the Johns Hopkins Health System [JHHS].)

**Rationale for use:** Although there is no high-quality evidence of benefit as of this writing, there is anecdotal descriptions from physicians in Spain and Italy evidence of rapid clinical improvement in COVID-19 patients following administration of tocilizumab. The administration, if effective, could prevent further decompensation and mechanical ventilation in severely ill patients.

### Guidance 3: Use of IL-6R or IL-6 Antibodies in Treatment of COVID-19

- **If a clinical trial of immune modulator therapy for COVID-19 is available, clinicians should seek enrollment for patients with COVID-19.** Clinical trial participation offers patients the best chance of receiving these agents. The use of these agents outside of a trial may be considered ONLY if no clinical trial is available or if patients do not meet eligibility criteria.
- **Limited availability:** The supply of tocilizumab and other anti-IL-6 receptor mAbs is very limited. The supply on hand and the availability for ordering are assessed daily.
- **Approval for use is required:** For use in COVID-19 patients, tocilizumab is restricted to approval by the **JHHS Formulary COVID Drug Approval Committee**. The Committee membership includes Brent Petty (JHH), Amy Knight (JHBMC), Ayesha Kahlil (HCGH), Leo Rotello (SH) and Mark Abbruzzese (SMH). Patient cases being requested for approval should meet the minimum criteria outlined in the *JHMI Clinical Guidance for Available Pharmacologic Therapies for COVID-19*.

## Guidance 3: Use of IL-6R or IL-6 Antibodies in Treatment of COVID-19

**Candidates for Treatment**

- Patients with COVID-19 and CRS who are at high risk of *severe* CRS may be considered for immune modulatory therapy if a clinical trial is not available; the suggested minimal criteria follows below. **All recommendations for treatment will be evaluated on an individual basis by the JHHS Formulary COVID Drug Approval Committee. Contact your institutional Committee member (noted above) to initiate discussion.**

☑ **Patients must meet the minimal criteria listed in each column [for either Row A or Row B] to be considered for evaluation by the COVID Drug Approval Committee.**

☑ **Priority is given to patients with progressive decline who are at risk of needing mechanical ventilation or who have been receiving mechanical ventilation for <24 hours.**

| Any 1 of these criteria | PLUS any 1 of these signs persistently and at time of assessment | PLUS all of these laboratory criteria[13,73,74] |
|---|---|---|
| **A. Low physiologic reserve due to:**<br>• Age ≥65 years ***or***<br>• Cardiomyopathy or coronary artery disease ***or***<br>• Lung disease ***or***<br>• Stem cell or organ transplant recipient ***or***<br>• End-stage renal disease (ESRD) | • Fever ≥39° C ***or***<br>• Hypotension (decrease in mean arterial pressure [MAP] by 10 mm Hg) ***or***<br>• *Progressive* hypoxemia sufficiently severe to require 4 to 6 liters of oxygen to maintain oxygenation ***or***<br>• Sustained respiratory rate >30 breaths/min | • IL-6 level* >100 pg/mL or a 5-fold increase from a prior level<br>**OR**<br>• All of the following:<br>– D-dimer level >1 µg/mL ***and***<br>– CRP level ≥10 mg/mL ***and***<br>– Ferritin level >1000 ng/mL |
| **B. <65 years** | • Fever ≥39° C ***and***<br>• Hypotension (decrease in MAP by 10 mm Hg) ***and***<br>• *Progressive* hypoxemia sufficiently severe to require 4 to 6 liters of oxygen to maintain oxygenation ***and***<br>• Sustained respiratory rate >30 breaths/min | • IL-6 level* >100 pg/mL or 5-fold increase from a prior level<br>**OR**<br>• All of the following:<br>– D-dimer level >1 µg/mL ***and***<br>– CRP level ≥10 mg/mL ***and***<br>– Ferritin level >1000 ng/mL |

*At the time of this writing, IL-6 testing is available for send-out testing when ordered through the Epic system or at the JHMI clinical immunology laboratory through the use of the Paper Form 4 (Pathology/Immunology). Turn-around time is faster using the JH laboratory.

**Dosing**

- Tocilizumab (preferred): 8 mg/kg once intravenously (IV) x one dose.[75]
  - Maximum dose should not exceed 800 mg.
  - Round dose to the nearest vial size (discuss with pharmacy).

**Guidance 3: Use of IL-6R or IL-6 Antibodies in Treatment of COVID-19**

  - IL_6 levels should not be checked after administration of tocilizumab because this agent leads to upregulation of IL-6 expression.[75]
  - **Supply based on availability.**
- Siltuximab (alternative): 11 mg/kg once IV once intravenously (IV) x one dose.
  - Maximum dose should not exceed 1100 mg.
  - Round dose to the nearest vial size (discuss with pharmacy).
  - **Supply based on availability.**

**Monitoring**

- If a mAb is administered, clinicians should order tuberculosis (TB) screening, using T-SPOT.TB or QuantiFERON Gold, if screening has not been performed within the past 6 months. If results are positive, clinicians should refer patients for follow-up with an infectious diseases clinician who can establish a management plan for latent TB infection once COVID-19 is resolved.
  - mAb administration should **NOT** be delayed pending results of TB screening.
- Hepatitis B virus (HBV) testing and prophylaxis are not generally required for short duration administration of tocilizumab. If a patient is taking other immunosuppressive medication(s) and has known positive hepatitis B surface antigen (HBsAg), seek consultation with a clinician from Infectious Diseases.

**Evidence:** Severe CRS ("cytokine storm") occurs in some patients with COVID-19.[62,63] Serum studies in these patients have found increased levels of cytokines, including IL-6, IL-10, IL-2R, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-alpha (TNF-α), that decline as patients recover.[76] Lymphopenia has also been reported, with a decline in CD4+ T cells and CD8+ T cells.[76] This cytokine and lymphocyte profile has some similarities to that seen in CAR-T–associated CRS.[66,77-80] Nonspecific inflammatory markers, including D-dimer, CRP, and ferritin are elevated in patients with CAR-T–associated CRS and with COVID-19–associated CRS.[72,81] CAR-T– and COVID-19–associated CRS also have overlap with macrophage activation syndromes, such as hemophagocytic lymphohistiocytosis.[82]

Given the apparent CRS similarities, it is plausible that tocilizumab might have the same benefit in the treatment of COVID-19 as it does in CAR-T. Tocilizumab is an IL-6 receptor blocker that is FDA-approved for treatment of CAR-T–associated CRS. Its use in the treatment of COVID-19 has been described in anecdotal reports from physicians in Spain and Italy. In China, 21 patients were treated with tocilizumab, and a majority had a striking improvement in oxygen requirement within 24 hours post-administration.[72] This may suggest that that IL-6 inhibition plays a role in COVID-19. Of note, most of the patients in the study from China also received steroids and LPV/RTV before receiving tocilizumab. Several of these case series used a dose of 8 mg/kg. This dosing is supported by data on more rapid clearance of tocilizumab during CRS compared to healthy volunteers, by the standard dose for CAR-T CRS, and by the concentration- dependent half-life.[75]

Siltuximab and sarilumab (IL-6 inhibitors) and anakinra (IL-1 inhibitor) have a theoretical benefit in the treatment of COVID-19–associated CRS and have the greatest similarity in effectiveness to tocilizumab. Some experts have considered these agents as alternatives if tocilizumab is unavailable. A case series of use of siltuximab has been reported from Italy.[83]

**Risks, adverse effects, and toxicity:** Tocilizumab and other mAbs have FDA black box warnings for the risk of severe infections that can lead to hospitalization and death.[84] Long-term use of such mAbs increases the risk of bacterial, mycobacterial, and fungal infections and reactivation of herpes simplex

and herpes zoster.[84] Notably, there are reports of an increased risk for TB and HBV reactivation in patients with rheumatologic diseases and long-term mAb use; these are not believed to be significant risks with a single dose.[85-87] However, there may be a risk of worsening of bacterial infections with short-term use.[88] Patients with known and not yet controlled infection (e.g., bacteremia) should not receive mAbs until the bacterial infection is controlled. Antimicrobial prophylaxis should be continued in patients who are currently receiving it. It may be reasonable to restart antimicrobial prophylaxis for those in whom it was recently discontinued.

**Adverse effects:** The following adverse effects have been reported:[84]

- Infusion-related reactions
- Gastrointestinal (diarrhea, abdominal pain, gastric ulcer, stomatitis)
- Asymptomatic liver enzyme elevations
- Headache
- Hypertension
- Hematologic disorders (thrombocytopenia, leukopenia; nadir 2 to 5 days after infusion)
- Increased serum bilirubin, nephrolithiasis
- Rash
- Gastrointestinal perforation (typically secondary to diverticulitis)
- Hypersensitivity reactions (including anaphylaxis): <1% in long-term use and upon administration of the first dose

## C. Convalescent Plasma or Serum-Containing Neutralizing Antibodies for Treatment of COVID-19

**Rationale for use:** The plausibility of convalescent plasma for treatment of COVID-19 is based on the treatment of infections and post-exposure prophylaxis for hepatitis A and B viruses, mumps, polio, measles, and rabies.[89,90] Some studies have suggested benefit in the treatment of influenza, SARS-CoV-1, and MERS-CoV.[91,92] A case series of 5 patients with COVID-19 suggested benefit.[93]

**Note:** The FDA has approved investigational use of convalescent plasma but the FDA does not supply the plasma; clinicians must procure it from a blood bank. The JH blood bank does not have COVID-19 convalescent plasma as of this writing. See: U.S. FDA Investigational COVID-19 Convalescent Plasma - Emergency INDs.

**Risks:** The risks associated with use of convalescent plasma include pathogen transmission, allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI).[94,95]

**Inclusion criteria:** The FDA has authorized an eIND application for expanded access to convalescent plasma for patients who meet the following criteria (as for any IND use, informed consent is required):

- Laboratory-confirmed COVID-19 ***and*** severe or immediately life-threatening complications of COVID-19
- Severe complications of COVID-19 include any of the following:
  - Dyspnea
    - Respiratory rate ≥30 breaths/minute
    - SaO2 ≤93%
    - Arterial partial pressure (PaO2) to fraction of inspired oxygen (FiO2) <300 mm Hg
    - Lung infiltrates >50% within 48 hours (imaging modality not specified in FDA eIND)
  - Life-threatening complications of COVID-19 include any of the following:

- Respiratory failure
- Septic shock
- Multi-organ failure

## D. Intravenous Immune Globulin (IVIG)

☑ **IVIG should only be used for COVID-19 in the setting of a clinical trial.**

**Rationale for use:** IVIG (non-convalescent) is used to modulate immune response by interacting with antibodies and complement and blocking receptors on immune cells.[96] IVIG has been used in treatment of multiple conditions to control pathogenic inflammation,[97] including SARS and COVID-19. A case series of 3 patients reported on the use of IVIG at the point of clinical deterioration and presumed shift to cytokine dysregulation.[98] All 3 patients were admitted to the hospital with mild COVID-19 symptoms, but deteriorated clinically several days after admission. Within 1 to 2 days of IVIG administration, all 3 patients had clinical improvement. More robust clinical data are needed to understand whether IVIG has a therapeutic role in COVID-19.

## E. Other Potential Immunotherapies for COVID-19

☑ **The agents below should be used to treat COVID-19 only in the setting of a clinical trial.**

Additional cytokine pathway targets that may have value in managing COVID-19 are listed and discussed below. These agents have been used in isolated CAR-T case scenarios (unpublished), treatment of COVID-19 (unpublished), or treatment of macrophage activation syndrome, or are being tested in clinical trials for COVID-19 (clinicaltrials.gov). At present, there is a lack of available data on their use for treatment of COVID-19. The theoretical justification for the use of these agents is described below.

**Janus kinase (JAK) inhibitors:** The JAK inhibitors ruxolitinib and fedratinib are FDA- approved for use in treatment of myelofibrosis and polycythemia vera. Ruxolitinib results in the downregulation of TNF-α, IL-5, IL-6, and IL-1B in T cells in vitro and in vivo.[99] Hence, these inhibitors may be useful against uncontrolled inflammation, such as that seen with COVID-19.

**Anti-IL1:** Anakinra is an IL-1 receptor antagonist that blocks the biologic activity of IL-1. Given the role of monocyte-derived IL-1 and IL-6 in CAR-T–associated CRS,[78] anakinra is being explored as a treatment for severe adverse effects of CAR-T (see NCT04148430, NCT04205838).

**Anti–GM-CSF mAb:** Lenzilumab is an mAb that neutralizes human GM-CSF; in vitro data suggest it may limit CRS. A clinical trial in humans is currently underway (see NCT04314843). Given the role of GM-CSF in inflammation and COVID-19,[82] lenzilumab may potentially be useful in the management of COVID-19 (phase III trial synopsis submitted to FDA).

**Hydroxymethylglutaryl-CoA (HMG Co-A) reductase inhibitors (statins):** In addition to altering cholesterol synthesis, these agents have an anti-inflammatory role. Statins may modify SARS-CoV-2 mediated inflammation.[100]

**TNF-α inhibitor:** Etanercept is a TNF-α blocker with limited experience in CAR-T–associated CRS. One reported case of CART-T–associated CRS did not improve with etanercept use.[101] Based on this limited experience, etanercept is not presently recommended for treatment of COVID-19.

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