JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19

Updated April 20, 2020, and replaces the document of April 14, 2020; COVID-19 Treatment Guidance Writing Group of Johns Hopkins University and Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

Contents

WHAT'S NEW? April 20, 2020 Update

- **Chloroquine no longer included:** Information about potential use of chloroquine has been removed because the agent is not available for ordering at Johns Hopkins, and it is not being used for treatment of patients with COVID-19 within the Johns Hopkins Health System.

- **New recommendation:** The writing group now recommends daily follow-up electrocardiogram (ECG) for all patients treated with hydroxychloroquine throughout the duration of treatment.

- **Updated criteria for consideration of treatment with tocilizumab:** Criteria for consideration now include any patient with suspected, evolving cytokine hyperinflammatory syndrome (based on specific clinical signs and laboratory values) who is ≥18 years old, and particularly if any factor is present that may increase the risk of poor outcomes.

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). This guidance provided is based on current knowledge, experience, and expert opinion. The goal is to establish and promulgate a standard approach to **considering use of pharmacologic agents for** JHMI 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.

For non-JHH specific guidelines, the Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 are now available and include a systematic assessment of available evidence.

RESOURCES FOR JOHNS HOPKINS CLINICIANS

- VTE Prophylaxis for COVID Positive Patients (intranet or uCentral app)

- Clinical Guidance for Critical Care Management of Patients with COVID-19 Infection

- JHH and JHBMC Discharge Guidelines for COVID Positive Patients Still on COVID Isolation (intranet)

- Johns Hopkins Medicine COVID-19 Clinical Resources (intranet)

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 regularly, and guidance will be updated as needed. The Johns Hopkins Health System community should feel free to provide comments to: C19Workgrp@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 clinical trials when they are available.

- **Guidance is based on expert opinion:** At the time of this writing, there are minimal available clinical data to support recommendations for the use of any specific pharmacologic treatment for patients with COVID-19. Existing data are drawn mostly from in vitro and nonrandomized (often unpublished) studies, or are extrapolated from animal models of related coronaviruses.

- **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 providing drugs only within the context of a therapeutic trial to providing drugs with theoretical but possible benefit if risks of adverse reactions are deemed acceptable.

- **This guidance applies only to the treatment of inpatients:** The writing group does not recommend outpatient treatment of patients with COVID-19 with off-label use of hydroxychloroquine, tocilizumab, or any of the agents noted in recommendations 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 care team.

II. Participation in Clinical Trials Is Strongly Recommended

A. Rationale

Multiple agents have theoretical value in the management of COVID-19 disease; however, 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 low quality evidence 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

Table: Clinical Trials and Investigational Drugs Available at Johns Hopkins Hospital			
Trial Name, Title, NCT ID and Link	**Drug(s)**	**Setting**	**Notes**
Active Trials			
- **Name:** Adaptive COVID-19 Treatment Trial (ACTT) - **Official Title:** A Multicenter, Adaptive, Randomized Blinded Controlled Trial of	- Remdesivir intravenous - Placebo	- Inpatient	- The study team will screen all patients who test positive for COVID-19 for eligibility, and the attending physician will

Table: Clinical Trials and Investigational Drugs Available at Johns Hopkins Hospital			
Trial Name, Title, NCT ID and Link	**Drug(s)**	**Setting**	**Notes**
the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults • **NCT ID and link:** 04280705 • See below for more information about remdesivir.			be contacted regarding potential enrollment of eligible patients.
• **Name:** (Substudy) DAS181 for COVID-19 • **Official Title:** DAS181 for COVID-19: a Multicenter, Randomized, Placebo-Controlled, Double-Blind Study • **NCT ID and link:** 03808922 • See below for more information about DAS181.	• DAS181 • Placebo	• Inpatient	• The study team will screen all patients in COVID-19 medical wards for eligibility, and the attending physician will be contacted regarding potential enrollment of eligible patients.
Pending Trials			
• **ACTG 5395 (HAz COVID)** • **Official Title:** A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy of Hydroxychloroquine (HCQ) and Azithromycin to Prevent Hospitalization or Death in Persons with COVID-19	• HCQ plus azithromycin • Placebo	• Outpatient	• Anticipated start late April
• **ACTG C5396** • **Official Title:** Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Hydroxychloroquine Monotherapy and in Combination with Azithromycin in Patients Hospitalized with Moderate and Severe COVID-19 Pneumonia	• HCQ plus placebo • HCQ plus azithromycin • Double placebo	• Inpatient	• Start date May 1
• **Convalescent Plasma COVID-19 Neutralizing titer not required** • See below for more information about convalescent plasma	• Convalescent plasma • Open label		• Emergency investigational new drug (eIND) through the U.S. Food and Drug Administration (FDA) for

Table: Clinical Trials and Investigational Drugs Available at Johns Hopkins Hospital			
Trial Name, Title, NCT ID and Link	**Drug(s)**	**Setting**	**Notes**
			convalescent plasma use in severe COVID-19
• **Convalescent Plasma COVID-19 - Containing Neutralizing Antibodies (RCT)** • See below for [more information about convalescent plasma](#)	• Convalescent plasma • Control plasma	Outpatient	• IND • Post-high-risk-exposure prophylaxis
• **Convalescent Plasma COVID-19 - Containing Neutralizing Antibodies (RCT)** • See below for [more information about convalescent plasma](#)	• Convalescent plasma • Control plasma	Outpatient	• IND • Outpatient RNA detection positive with COVID-19

III. Use of Drugs with Possible but Unproven Antiviral Activity for Treatment of COVID-19

A. Hydroxychloroquine (HCQ)

Background: The recommendations that follow are based on the very limited evidence discussed below. Although this writing group does not recommend off-label use of HCQ to treat hospitalized patients with COVID-19, the group recognizes that after weighing the known risks of use, clinicians may decide to prescribe HCQ. The recommendations below are to guide such use, with the strong caveat that HCQ's efficacy in treatment of COVID-19 is not clear. Experience with other acute viral infections suggests that if HCQ does have clinically significant antiviral activities, it is likely to be more effective if initiated as soon as possible.[1] HCQ is generally well tolerated.[2]

Recommendations for Consideration, Administration, and Monitoring of HCQ Treatment

☑ After careful assessment of known risks and low-quality evidence of benefit, clinicians may consider HCQ therapy only for hospitalized patients who have confirmed COVID-19 and do not require either intensive care unit management or mechanical ventilation.
   – If HCQ is found to have a benefit, it will most likely be early in the course of disease.
☑ Clinicians should not prescribe HCQ for any patient who:
   – Requires intensive care unit management or mechanical ventilation.
   – Has multiorgan failure (new impairment in pulmonary, kidney, liver, and cardiovascular function). This is due to cardiotoxicity concerns with severe COVID-19 and HCQ use.[3,4]
   – Has a QTc >500 ms at baseline (or QTc >550 ms in patients with wide QRS >120 ms),[3] documented cardiomyopathy, or myocarditis.[4] If the QTc increases to >500 ms, clinicians should discontinue HCQ treatment.

Recommendations for Consideration, Administration, and Monitoring of HCQ Treatment

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

☑ Outside of a clinical trial, clinicians should not prescribe azithromycin or fluoroquinolones concurrently with HCQ because of the additive risk for QTc prolongation.[8]

   – If atypical coverage is needed for the treatment of community-acquired pneumonia, doxycycline can be used in place of these agents.

☑ Clinicians should not require screening for G6PD deficiency or retinopathy before initiating HCQ treatment.

   – Screening is not recommended since the short-term use of HCQ COVID-19 treatment is unlikely to cause hemolysis or ocular toxicities.

   – Retinal injury has been associated with long-term HCQ therapy; the American Academy of Ophthalmology does not recommend retinal screening before short-term use; use is contraindicated in patients with existing retinal pathology.[7]

☑ 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.

     · No dosage adjustment is necessary for renal or liver impairment.

     · 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.

☑ Clinicians should obtain daily follow-up electrocardiogram (ECG) in all patients throughout the duration of HCQ administration.

☑ Clinicians should not continue HCQ treatment in a patient who is discharged from inpatient care before having completed the 5-day course of HCQ treatment.

   – Outpatient use of HCQ is recommended only for patients who are participating in a clinical trial.

Review of clinical data and limited evidence: HCQ and chloroquine have in vitro activity against SARS-CoV-2 and some other viruses.[9,10] 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.[11-13] The clinical data discussed below are mostly from unpublished reports that have not been peer reviewed.

- **Viral shedding:** A retrospective study compared viral shedding in 36 patients treated with HCQ, HCQ plus azithromycin, or neither. Reduced viral shedding was found in the HCQ and HCQ plus azithromycin groups.[14] The lack of pair-wise comparisons and exclusion of patients on HCQ who had disease progression (i.e., death or admission to intensive care) are 2 of the many limitations of this study. A follow-up study assessed viral shedding in 80 patients who received HCQ plus azithromycin. Most patients had a negative viral load test by day 8.[15] In another French study, viral clearance was measured in 11 patients treated with HCQ plus azithromycin. In the 9 patients who remained under observation at day 5 or 6, 80% still had positive viral PCR results.[16] An RCT from China that included 30 patients, reported that 86% of HCQ and 93% of control patients had cleared viral shedding at day 7.[17] A larger (150 patients), open-label RCT from China reported negative viral PCR at 28 days in 85% of patients in the HCQ arm and in 81% of those who did not receive HCQ (conversion was also similar between groups at 4, 7, 10, 14, and 21 days as well).[18] These studies

demonstrate the heterogeneity of reports on viral shedding, and none of these studies, or others, have correlated viral shedding with clinical outcomes.

- **Clinical outcomes:** An open label RCT from China evaluated 62 patients with mild illness who were randomized to receive HCQ or usual care.[19] Fever resolved more rapidly in the HCQ group (2.2 days vs. 3.2 days), and there was greater radiographic improvement in pneumonia (81% vs. 55%; P=.05). This value of these results are limited by the quality of the study endpoints, the failure to describe the additional treatment patients were receiving (e.g., steroids, antiviral agents, and immunoglobulins), and by the use of fever resolution as a clinical endpoint given the known mild antipyretic activity of HCQ. A retrospective study of HCQ that used propensity weighting to compare patients who did and did not receive HCQ within 48 hours of hospitalization reported no difference in death or acute respiratory distress syndrome within 7 days.[20]

Safety: Since March 27, 2020, the French National Agency for the Safety of Medicine and Health Products (ANSM) has conducted pharmacovigilance surveys to monitor adverse effects of medications used to treat COVID-19. In a sub-analysis, ANSM found that 43 of all 53 cardiac adverse events occurred in patients receiving HCQ or HCQ plus azithromycin. These events included 7 cases of cardiac death, 12 rhythm disorders leading to syncope, and the rest prolongation of QT.[21]

Risks and adverse effects: The overall risks associated with HCQ are likely low but are unknown in treatment of COVID-19.[2] 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.[22] Given the concern for HCQ-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.[4] An additional risk is **hypoglycemia**, as described in multiple case reports.[23-27]

For patients hospitalized with COVID-19, without contraindications to HCQ use, the theoretical benefits could be considered by some clinicians to outweigh the risks of treatment; therefore, the decision must be discussed with the patient or the patient's surrogate. On the other hand, based on currently available data, it is 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 likely outweighs the potential benefit.

Long-term use of HCQ may be associated with **retinal toxicities**. Short-term use is generally not associated with retinal damage and may be used in people with preexisting retinal disease, such as diabetic retinopathy or macular degeneration. **Concurrent use of tamoxifen (also a retinal toxin) increases the risk of retinopathy.**[28]

The following common and transient adverse effects of HCQ have been reported in ≤1% of patients:[29-32]

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

HCQ is safe for use in pregnancy (Class B).[33,34]

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 (see NCT04308668).

B. DAS181

DAS181 is a recombinant sialidase fusion protein. It cleaves sialic acid, which is important as part of binding to cell surfaces in the respiratory tract, thus potentially decreasing the ability for viruses to enter cells. It has potential antiviral activity against parainfluenza, metapneumovirus, enterovirus, and influenza. Because coronaviruses also have a sialic acid-binding domain, there is the potential for activity against SARS-CoV-2.[35] There are anecdotal reports of DAS181 use in non-research settings in China for treatment of COVID-19.

DAS181 is administered via a nebulizer once daily for 7 to 10 days. The drug has been studied in Phase I and Phase II clinical trials and in compassionate use, with good tolerability.[36] Reported potential side effects include elevations in alkaline phosphatase, transaminases, creatinine phosphokinase, lactate dehydrogenase, and prothrombin time. Patients also reported dysgeusia, diarrhea, and throat irritation. Bronchospasm has also been reported from clinical trials.

C. Remdesivir

Remdesivir is an intravenous (IV) medication that has in vitro activity against SARS-CoV-2 and other coronaviruses.[37,38] 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.[39] In a mouse model, remdesivir was effective when tested as a treatment for SARS-CoV-1,[38] and it was effective when tested in both a mouse and a primate model for MERS-CoV.[40,41] Compassionate use of remdesivir has also been described for SARS-CoV-2.[42,43] See Emergency Access to Remdesivir Outside of Clinical Trials (gilead.com) for the most up-to-date information regarding expanded access use of remdesivir.

D. Agents with Speculative Antiviral Effect against COVID-19

Recommendation for Agents to Avoid as Treatment for 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.
  – There is no evidence that any of the following agents are harmful in patients with COVID-19 when used to treat other conditions.
    · Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (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 (described below).

- **ACE inhibitors or ARBs:** Host cell entry by SARS-CoV-2 appears to depend on the ACE2 receptor.[44] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulate ACE2 expression,[45] 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.[46]

  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.[14] Note: The journal to which this study was initially submitted has rejected the paper. No efficacy was found in a study of azithromycin against MERS-CoV.[47]

- **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.[48] 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.[49,50] 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.[50] 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.[49] 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.[51] 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.[52] 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.[53]

- **Lopinavir/ritonavir (LPV/RTV):** This combination has weak in vitro activity against SARS-CoV-2. An RCT from China reported no clinical benefit among patients hospitalized with COVID-19 who were given LPV/RTV (starting a median of 13 days into illness).[54] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[55] A nonrandomized

retrospective study from China described fever resolution and laboratory findings from 42 patients who received LPV/RTV and 5 who did not. Timing of LPV/RTV treatment was not described. Among a subset (number not provided) of patients with fever, there was no difference in the rate of temperature decline, but the time to a normal body temperature was reported as shorter in the LPV/RTV group. Several laboratory markers (C-reactive protein [CRP], lymphocyte count) also appeared to be better in the LPV/RTV group. The very small sample size of patients not treated with LPV/RTV limits the value of this report.[56]

- **Nitazoxanide:** This agent has been tested in vitro against MERS-CoV and SARS-CoV-2 and found to have activity.[57] 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.[58]

- **Umifenovir:** This agent was routinely used in China to treat patients with COVID-19.[59] 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.[60] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[61]

- **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 acute respiratory distress syndrome (ARDS).[62] 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 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.[63]

IV. Considerations for Use of Immune Modulatory Agents to Treat COVID-19

A. IL-6R or IL-6 Monoclonal Antibodies

Supply: The supply of tocilizumab and other anti-IL-6 receptor mAbs is limited, and the availability for ordering is assessed daily. Clinical trial participation offers patients the best chance of receiving these agents.

Criteria for Consideration of COVID-19 Treatment with IL-6R or IL-6 Antibodies

- **Patients may 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 trial participation.**

- Clinicians may consider patients with COVID-19 who are suspected of having an evolving cytokine hyperinflammatory syndrome for immune modulatory therapy if a clinical trial is not available. Anecdotal findings and expert opinion suggest that the drug may be most effective when clinical deterioration is identified prior to intubation. Priority for evaluation by the COVID Drug Approval Committee will be given to patients who meet the minimal criteria below.

1. The patient is ≥18 years old with suspected, evolving hyper-inflammatory syndrome.	2. AND the patient has any one of these clinical signs:	3. AND patient laboratory values include:

- The following factors may increase a patient's risk of poor outcomes (this list may not be comprehensive)
 	
  – Age ≥65 years old
  – Black race
  – Solid organ transplant recipient
  – Stem cell transplant within the previous 12 months
  – Cardiac disease
  – Diabetes
  – Obesity (BMI >30)
  – Structural lung disease
  – End-stage kidney disease
  – Advanced liver disease
	- Fever ≥38.3° C *and*
	
	- Hypotension (decrease in mean arterial pressure [MAP] by 10 mm Hg) *or*
	
	- *Progressive* hypoxemia sufficiently severe to require at least 4 liters of oxygen to maintain PaO2>92% *or*
	
	- Sustained respiratory rate >30 breaths/min.
		- An IL-6 level >100 pg/mL *or* a 5-fold increase from a prior level
		
		  – OR
		
		- All of the following:
		
		  – D-dimer level >1 µg/mL *plus*
		  – CRP level ≥10 mg/mL *plus*
		  – Ferritin level >750 ng/mL

- **If treatment with an immunomodulator is desired and the patient meets the minimal criteria noted above, approval for the use of tocilizumab is required:** Use of tocilizumab in patients with COVID-19 is restricted to approval by the Johns Hopkins Health System (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 below. All recommendations for treatment will be evaluated on an individual basis by the JHHS Formulary COVID Drug Approval Committee. Contact the committee member for your institution, noted above, to initiate discussion.

Recommendations for Use of Immune Modulatory Agents to Treat COVID-19

☑ **mAbs:** Tocilizumab is the preferred mAb; supply is based on availability.

– **Dosing:** If a patient is approved for tocilizumab therapy (preferred*), the clinician should dose it as 8 mg/kg intravenously (IV) x one dose.[81-83]

· Maximum dose should not exceed 800 mg.

· Round dose to the nearest vial size (discuss with pharmacy).

· Clinicians should not check IL-6 levels after administration of tocilizumab because this agent leads to elevated IL-6 levels.[81]

– 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 generally **not** 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.

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

☑ **Other immune modulators:** Use of the following agents as treatment for COVID-19 is recommended only in the setting of a clinical trial (see Section E for details on potential mechanism of action):

– Intravenous immune globulin (IVIG)

– Convalescent plasma or serum-containing neutralizing antibodies

– Janus kinase (JAK) inhibitors

– Anti-IL1

– Anti–GM-CSF mAb

– Hydroxymethylglutaryl-CoA (HMG Co-A) reductase inhibitors (statins)
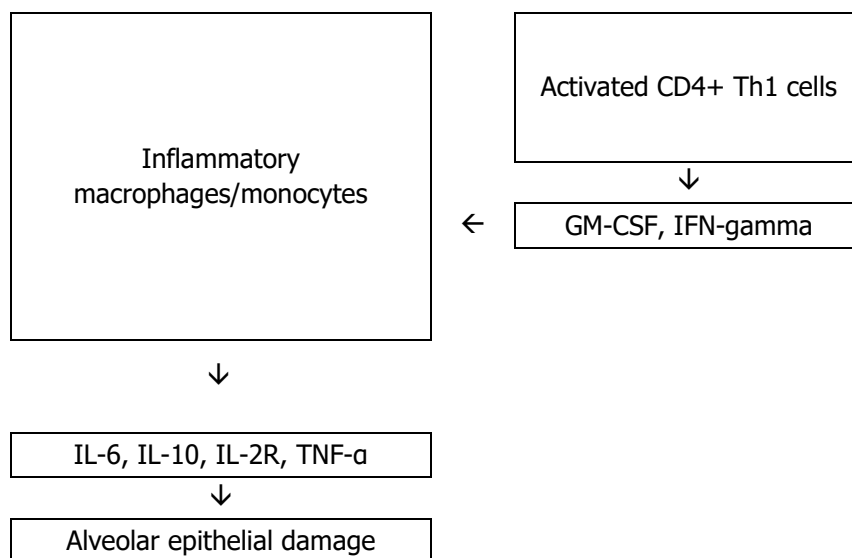
– TNF-α inhibitors

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*Alternative: Siltuximab (supply based on availability) is administered as 11 mg/kg intravenously (IV) x one dose.[84] The dose should be rounded to the nearest vial size in consultation with the pharmacy, and the maximum dose should not exceed 1100 mg.

Background: The natural history of severe COVID-19 appears to be an initial viral pneumonia followed in some patients by a hyperinflammatory syndrome-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.[64,65] The hyperinflammatory syndrome can occur approximately 5 to 10 days into the disease course (Figure 1). It 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, CRP, and ferritin. Patients may progress to multiorgan failure as a result of the CRS or uncontrolled viral infection.[66] Microvascular thrombosis and venous thromboembolism have also been reported and may be a separate or related pathway to respiratory compromise.[67-69]

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 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[70,71]

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┌─────────────────────────┐        ┌─────────────────────────────┐
│                         │        │                             │
│                         │        │    Activated CD4+ Th1 cells │
│     Inflammatory        │        │                             │
│  macrophages/monocytes  │        └─────────────────────────────┘
│                         │                      ↓
│                         │  ←     ┌─────────────────────────────┐
│                         │        │      GM-CSF, IFN-gamma       │
└─────────────────────────┘        └─────────────────────────────┘
            ↓

┌─────────────────────────┐
│  IL-6, IL-10, IL-2R, TNF-α │
└─────────────────────────┘
            ↓
┌─────────────────────────┐
│  Alveolar epithelial damage │
└─────────────────────────┘
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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

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.[77]

Although published clinical data on and experience with management of cytokine release syndrome (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 JHHS.)

Although there is no high-quality evidence of benefit as of this writing, there are anecdotal descriptions and case series from physicians in Spain and Italy 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.

Review of evidence: Severe hyperinflammatory syndrome occurs in some patients with COVID-19.[64,65] 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.[85] Lymphopenia has also been reported, with a decline in CD4+ T cells and CD8+ T cells.[85] This cytokine and lymphocyte profile has some similarities to that seen in CAR-T–associated CRS.[71,86-89] Nonspecific inflammatory markers, including D-dimer, CRP, and ferritin are elevated in patients with CAR-T–associated CRS and with COVID-19–associated hyperinflammatory syndrome.[77,90] CAR-T-associated CRS and COVID-19-associated hyperinflammatory syndrome also have overlap with macrophage activation syndromes, such as hemophagocytic lymphohistiocytosis.[91]

Given the apparent 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.[77] Additional case series have supported the overall safety of this agent.[92] This may suggest that IL-6 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,[82] and by the concentration-dependent half-life.[81]

Siltuximab and sarilumab (IL-6 inhibitors) and anakinra (IL-1 inhibitor) have a theoretical benefit in the treatment of COVID-19–associated hyperinflammatory syndrome 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.[84]

Risks and adverse effects: Tocilizumab and other mAbs have FDA black box warnings for the risk of severe infections that can lead to hospitalization and death.[93] Long-term use of such mAbs increases the risk of bacterial, mycobacterial, and fungal infections and reactivation of herpes simplex and herpes zoster.[93] 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.[94-96] However, there may be a risk of worsening of bacterial infections with short-term use.[97] 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.

The following adverse effects have been reported:[93]

- 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

B. Corticosteroids

An RCT of corticosteroids for bronchiolitis among children found no clinical benefit or notable harm.[72] A meta-analysis of 10 observational studies of corticosteroid use for influenza found that these agents may increase the risk of mortality.[73] Several published observational studies of corticosteroid use in the treatment of SARS-CoV-1 have reported adverse effects and no benefit.[74] A retrospective study from China compared 26 patients 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.[75] Steroids may have a role in managing septic shock or relative adrenal insufficiency and should be used as needed in critical care management.[76] 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 hyperinflammatory syndrome.

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

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.[98,99] Some studies have suggested benefit in the treatment of influenza, SARS-CoV-1, and MERS-CoV.[100,101] Several case series of small numbers of patients with COVID-19 suggested benefit.[102-104]

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.

Recovered COVID-19 patients may email (JHUcovidplasma@jhmi.edu) to begin the screening process for donation of convalescent plasma for use at Johns Hopkins.

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).[105,106]

D. Intravenous Immune Globulin (IVIG)

IVIG (non-convalescent) is used to modulate immune response by interacting with antibodies and complement and blocking receptors on immune cells.[107] IVIG has been used in treatment of multiple conditions to control pathogenic inflammation,[108] 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.[109] 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

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), 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 such as baricitinib, ruxolitinib, and fedratinib are FDA-approved for use in treatment of rheumatoid arthritis, myelofibrosis, or 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.[110] Hence, these inhibitors may be useful against uncontrolled inflammation, such as that seen with COVID-19 (see NCT04340232 and NCT04321993)

- **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,[87] anakinra is being explored as a treatment for severe adverse effects of CAR-T (see NCT04148430, NCT04205838).

- **Anti–GM-CSF mAb:** Lenzilumab is a 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,[91] 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.[111]

- **TNF-α inhibitor:** Etanercept is a TNF-α blocker with limited experience in CAR-T–associated CRS. One reported case of CAR-T–associated CRS did not improve with etanercept use.[112] Based on this limited experience, etanercept is not presently recommended for treatment of COVID-19.

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