JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19

Updated May 11, 2020, and replaces the document of May 4, 2020; COVID-19 Treatment Guidance Writing Group of Johns Hopkins University and The Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

Contents

WHAT'S NEW? May 11, 2020 Update

- **New section:** Timing of Treatment and Therapeutic Approach.
- **Expanded discussion:** Plausibility of use of convalescent plasma or serum-containing neutralizing antibodies.
- **Deletion:** Table of available clinical trials removed; please see: Johns Hopkins Institute for Clinical and Translational Research: Ongoing COVID-19 Research, including Expanded Access Protocols.

I. Purpose, Development, and Guiding Principles

A. Purpose

The purpose of this document is to provide pharmacologic treatment guidance for clinicians at The 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 the 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.

Available non-JHH-specific guidelines include those of the Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 (which include a systematic assessment of available evidence) and the NIH Coronavirus Disease (COVID-19) Treatment Guidelines.

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)
- Johns Hopkins Institute for Clinical and Translational Research: Ongoing COVID-19 Research, including Expanded Access Protocols

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.
- **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.

E. Participation in Clinical Trials Is Strongly Recommended

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.

Current approved therapeutic protocols for COVID-19: See Johns Hopkins Institute for Clinical and Translational Research: Ongoing COVID-19 Research, including Expanded Access

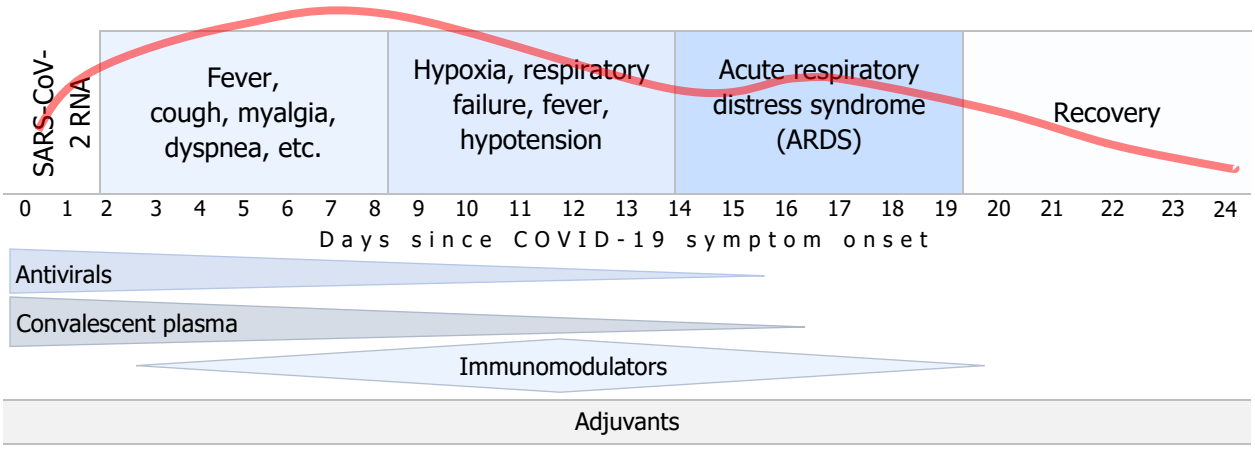
II. Timing of Treatment and Therapeutic Approach

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 may be characterized by fever, cough, fatigue, myalgia, and dyspnea. Radiographically, ground-glass opacities are seen in the lungs, along with lymphocytopenia, also commonly observed.[1,2] The hyperinflammatory syndrome can occur approximately 5 to 10 days into the disease course. 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,[3,4] and nonspecific markers of inflammation including D-dimer, CRP, and ferritin. Patients may progress to multiorgan failure as a result of the cytokine-mediated hyperinflammation or uncontrolled viral infection.[5] Microvascular thrombosis and venous thromboembolism have also been reported and may be a separate or related pathway to respiratory compromise.[6-8]

Serum studies in patients with hyperinflammatory syndrome 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.[9] Lymphopenia has also been reported, with a decline in CD4+ T cells and CD8+ T cells.[9] This cytokine and lymphocyte profile has some similarities to that seen in CAR-T–associated cytochrome release syndrome (CRS).[10-14] Nonspecific inflammatory markers, including D-dimer, CRP, and ferritin are also elevated in patients with CAR-T–associated CRS and with COVID-19–associated hyperinflammatory syndrome.[15,16] CAR-T-associated CRS and COVID-19-associated hyperinflammatory syndrome also have overlap with macrophage activation syndromes, such as hemophagocytic lymphohistiocytosis.[17]

The optimal timing for potential therapeutic agents is unknown. In this guidance, the timing for administration of pharmacologic agents is based on the type of medication and whether there is a potential for direct antiviral effect, or modulation of excessive cytokine response, or a nonspecific adjuvant impact on the host, as illustrated in the figure below.

Figure: Schematic of clinical course of severe COVID-19 with representation of SARS-CoV-2 RNA levels, common symptoms, and possible timing of therapeutic use of greatest benefit



III. Use of Drugs with Possible Antiviral Effects for Treatment of COVID-19

A. Convalescent Plasma or Serum-Containing Neutralizing Antibodies

Plausibility: Convalescent plasma has been used in China and the United States for the treatment of COVID-19. Several reported case series have suggested possible shorter duration of symptoms without apparent side effects.[18-20] Use of convalescent plasma as a treatment for COVID-19 is based on the principle of passive antibody therapy, which has been used as post-exposure prophylaxis and treatment for hepatitis A and B viruses, mumps, polio, measles, rabies, SARS-CoV-1, MERS-CoV, and Ebola.[21-25] The underlying mechanism of activity of convalescent plasma is principally antibody-mediated. Convalescent plasma contains antibodies to SARS-CoV-2 that may bind to and inactivate the virus, augment innate immunity through complement activation, and contribute to antibody-dependent cellular cytotoxicity of infected cells.[25]

Benefits and risks: Convalescent plasma is believed to be of the most significant benefit early in the course of the disease. When used to treat patients during the 2002 SARS-1 outbreak, convalescent plasma was more effective when administered within the first 14 days of symptom onset.

The risks associated with the use of convalescent plasma include pathogen transmission, antibody-dependent enhancement of infection,[25-27] allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI); all of which are rare.[26,27]

Standardization of neutralizing antibodies has not yet been established, and current testing is not specific to neutralizing antibodies, so some proportion of donor convalescent plasma may lack sufficient titers of neutralizing antibodies.

Availability: The FDA has approved the investigational use of convalescent plasma; hospitals are responsible for working with blood banks to source the plasma. Convalescent plasma is a limited resource, the availability of which is subject to supply. As of this writing, access at JHMI is available through a system-wide expanded access IND (start date TBD). Clinicians who wish to request convalescent plasma for the treatment of critical care patients should send an email to JHUcovidplasma@jhmi.edu. However, this treatment is likely to be most effective when used earlier in the course of COVID-19.

For more information, see U.S. FDA Recommendations for Investigational COVID-19 Convalescent Plasma and COVID-19 Expanded Access Program.

Plasma donation: Recovered patients who wish to be screened for donation of convalescent plasma for use at JHH should send an email to JHUcovidplasma@jhmi.edu.

B. DAS181

DAS181 is not available outside of clinical trials.

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.[28] 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, and all have shown good tolerability.[29] 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. Hydroxychloroquine (HCQ)

Recommendations for Consideration, Administration, and Monitoring of HCQ Treatment

- ☑ **HCQ is not recommended to treat patients with COVID-19 (outside of a clinical trial).**
  - 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.
- ☑ 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.[30,31]
  - Has a QTc >500 ms at baseline (or QTc >550 ms in patients with wide QRS >120 ms),[30] documented cardiomyopathy, or myocarditis.[31] If the QTc increases to >500 ms, clinicians should discontinue 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.
- ☑ Clinicians should not prescribe azithromycin or fluoroquinolones concurrently with HCQ because of the additive risk for QTc prolongation.[32]

Recommendations for Consideration, Administration, and Monitoring of HCQ Treatment

- 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.[33]

☑ If a clinician decides to prescribe HCQ after careful assessment of known risks and low-quality evidence of benefit, the following dosing scheme 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 electrocardiograms (ECGs) in all patients for 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.[34,35] 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.[36-38] 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.[39] 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.[40] In another French study, viral clearance was measured in 11 patients treated with HCQ plus azithromycin. In the 9 patients who remained under observation on day 5 or 6, 80% still had positive viral PCR results.[41] 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.[42] 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).[43]
- **Clinical outcomes:** An open-label RCT from China evaluated 62 patients with mild illness who were randomized to receive HCQ or usual care.[44] 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.[45] Another retrospective study of HCQ use across the United States Veterans Administration system reported on 368 patients who either received HCQ, HCQ plus azithromycin, or neither.[46] Patients who received just HCQ had the highest rate of mortality; mortality was lower and similar on those who received HCQ plus azithromycin or neither drug. Although the researchers adjusted for various factors, they included patients who received HCQ at any time during hospitalization for COVID-19, increasing the chance of confounding by indication. What can be concluded from the studies of the clinical outcomes is that there is neither sufficiently clear benefit nor clear harm associated with HCQ treatment for COVID-19.

Risks and adverse effects: The overall risks associated with HCQ are likely low but are unknown in treatment of COVID-19.[47] 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.[48] 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.[31] Furthermore, given the risk of arrhythmia overall, the U.S. Food and Drug Administration (FDA) recommends against the use of HCQ in outpatients with known cardiac arrhythmias.[49] An additional risk is **hypoglycemia**, as described in multiple case reports.[50-54]

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.[55]**

The following common and transient adverse effects of HCQ have been reported in ≤1% of patients:[56-59]

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

HCQ is safe for use in pregnancy (Class B).[60,61]

Safety: Since March 27, 2020, the French National Agency for the Safety of Medicine and Health Products (ANSM) has conducted pharmacovigilance surveys to monitor the 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.[62]

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).

D. Remdesivir

***As of this writing, Johns Hopkins Health System will not be receiving a supply of remdesivir from the federal government.**

Remdesivir is an intravenous (IV) medication that has in vitro activity against SARS-CoV-2 and other coronaviruses.[63,64] Remdesivir has been tested in humans for the treatment of Ebola virus infection and performed as well as ZMapp but was inferior to human monoclonal antibodies (mAbs).[65] In a mouse model,

remdesivir was effective when tested as a treatment for SARS-CoV-1,[64] and it was effective when tested in both a mouse and a primate model for MERS-CoV.[66,67] A double-blind, placebo-controlled clinical trial from China that included hospitalized patients who had a median of 10 days of symptoms reported no difference in clinical resolution by arm.[68] A small sample size and treatment administered in the late stage of disease are limitations of this study. The National Institute of Allergy and Infectious Disease issued a press release on results of the NIH-sponsored ACTT trial and reported a 31% faster time to recovery in patients receiving remdesivir compared to placebo.[69] The median duration of symptoms before patients received remdesivir was not provided. In its press release on the SIMPLE study, Gilead reported no difference in outcomes in an open-label study of 5-day and 10-day dosing of remdesivir in patients who did not require mechanical ventilation.[70]

On May 1, 2020, based on the preliminary results from the two U.S. studies noted above, the FDA issued an emergency use authorization (EUA) for remdesivir for the treatment of COVID-19.[71] This EUA does not imply FDA approval. Remdesivir is still considered an investigational drug, and it has not been approved for any indication, including COVID-19 treatment. The EUA criteria for the use of remdesivir in patients hospitalized for COVID-19 treatment and dosing are as follows:

Table 2: EUA for Use of Remdesivir* to Treat Hospitalized Patients with COVID-19[72]

Patient Status	Treatment Duration	Dosing and Administration
Receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	10 days	• Day 1 (loading dose): Remdesivir 200 mg IV • Days 2 through 9: Remdesivir 100 mg IV daily
SaO2 ≤94% on room air or supplemental oxygen required	5 days; if no improvement after 5 days, continue for an additional 5 days	• Day 1, loading dose: Remdesivir 200 mg IV • Days 2 through 5: Remdesivir 100 mg IV daily

*As of this writing, remdesivir is not available through this mechanism at JHMI. JHH has an institutional IND for expanded access use of remdesivir in pediatric patients (<18 years of age).

E. 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
  - Famotidine
  - Favipiravir (not FDA-approved or available in the United States)

Recommendation for Agents to Avoid as Treatment for COVID-19 Specifically
· 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.[73] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression,[74] leading to concerns of a theoretical risk with the 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.[75] The best evidence suggests either similar or improved outcomes among people on chronic ACE or ARB therapy who develop COVID-19.[76]

  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.

- **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.[39] A subsequent study reported no increase in viral clearance with HCQ plus azithromycin.[41] Subsequent works suggest no benefit and potential harm. A retrospective study of non-COVID-19 patients who received chronic HCQ (for rheumatologic reasons) and short courses of azithromycin for acute conditions identified an increased risk of cardiovascular mortality within 30 days of adding azithromycin.[32] No clinical efficacy was found in a study of azithromycin against MERS-CoV.[77]
- **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 had reported weak in vitro activity against SARS-CoV-2.[78] However, a more recent study reported no in vitro activity against SARS-CoV-2.[32] 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.[79]
- **Famotidine:** Famotidine is hypothesized to bind to SARS-CoV-2 papain-like protease and inhibit replication. Unpublished anecdotes have suggested possible value in treating COVID-19, leading to a trial of high-dose IV famotidine for COVID-19.[80]
- **Favipiravir**: This inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.[81,82] 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.[82] 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.[81] 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.[83] These findings are intriguing, but correlation with clinical outcomes in humans is required before the use of INDO can be recommended for the 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.[84] 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.[85]
- **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).[86] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[87] A nonrandomized retrospective study from China described fever resolution and laboratory findings from 42 patients who received LPV/RTV and 5 who did not. The 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. The very small sample size of patients not treated with LPV/RTV limits the value of this report.[88] A small RCT that randomized 86 patients with mild COVID-19 to one of 3 arms—LPV/RTV, umifenovir, or control—reported no difference in the rate of nucleic acid clearance, resolution of fever, resolution of cough, or improvement in chest x-ray.[89]
- **Nitazoxanide:** This agent has been tested in vitro against MERS-CoV and SARS-CoV-2 and found to have activity.[90] 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.[91]
- **Umifenovir:** This agent was routinely used in China to treat patients with COVID-19.[92] 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.[93] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[94]
- **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).[95] 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.[96]

IV. Use of Immunomodulators 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.

Table 3: 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 before 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 COVID-19 hyperinflammatory syndrome.	**2. AND the patient has *progressive* hypoxemia* *plus* one of the following:**	**3. AND the patient's 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	• Sustained respiratory rate >30 breaths/min. ***or*** • Hypotension (decrease in mean arterial pressure [MAP] by 10 mm Hg) ***or*** • Fever ≥38.3° C *sufficiently severe to require at least 4 liters of oxygen to maintain PaO2>92%	An IL-6 level >80 pg/mL **OR** • All of the following: – D-dimer level >1 µg/mL ***plus*** – CRP level ≥10 mg/dL ***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 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 above. 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.[97-99]
    - 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.[97]
  - 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 the 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

*Alternative: Siltuximab (supply based on availability) is administered as 11 mg/kg intravenously (IV) x one dose.[100] The dose should be rounded to the nearest vial size in consultation with the pharmacy, and the maximum dose should not exceed 1100 mg.

Tocilizumab: Tocilizumab is an IL-6 receptor blocker that is FDA-approved for the treatment of chimeric antigen receptor T-cell therapy (CAR-T)–associated CRS. Because COVID-19-associated hyperinflammation is similar to CAR-T CRS, it is plausible that tocilizumab, which is widely used to treat CAR-T CRS, might be beneficial in the treatment of COVID-19. It also suggests that IL-6 may play a role in COVID-19. To date, though, the clinical evidence of immune modulatory therapy benefit for patients with COVID-19 is limited to analogy, anecdotes from clinicians in Spain and Italy, and case series, including one from China that reported a striking and rapid improvement in oxygen requirement in the majority of 21 patients treated with tocilizumab.[15] 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,[98] and by the concentration-dependent half-life.[97] Additional case series have supported the overall safety of this agent.[101]

Because it has been used more often at JHMI and in publically available case series[15], tocilizumab is the preferred agent when, having weighed the risks and unproven benefit, clinicians wish to seek approval for the use of an IL-6R or IL-6 inhibitor.

Other mAbs: Although published clinical data on and experience with management of CRS-associated with either 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. 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. A case series of use of siltuximab has been reported from Italy.[100] Some experts have considered these agents as alternatives if tocilizumab is unavailable; however, as of this writing, sarilumab and anakinra are not available for use in treating COVID-19 throughout the JHHS.

Clazakizumab, also an IL-6 inhibitor under investigation for use in COVID-19. For more information, see ICTR Current Approved Therapeutic Protocols for COVID-19 and NCT04363502.

Lenzilumab neutralizes human granulocyte-macrophage colony-stimulating factor (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,[17] lenzilumab may potentially be useful in the management of COVID-19.

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.[102] Long-term use of such mAbs increases the risk of bacterial, mycobacterial, and fungal infections and reactivation of herpes simplex and herpes zoster.[102] 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.[103-105] However, there may be a risk of worsening of bacterial infections with short-term use.[106] 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:[102]

- 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.[107] A meta-analysis of 10 observational studies of corticosteroid use for influenza found that these agents may increase the

risk of mortality.[108] Several published observational studies of corticosteroid use in the treatment of SARS-CoV-1 have reported adverse effects and no benefit.[109] 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.[110] Steroids may have a role in managing septic shock or relative adrenal insufficiency and should be used as needed in critical care management.[111] 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.

D. Intravenous Immune Globulin (IVIG)

IVIG (non-convalescent) is used to modulate the immune response by interacting with antibodies and complement and blocking receptors on immune cells.[112] IVIG has been used in the treatment of multiple conditions to control pathogenic inflammation,[113] 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.[114] 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 the 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 the 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.[115] 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,[11] anakinra is being explored as a treatment for severe adverse effects of CAR-T (see NCT04148430, NCT04205838).
- **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.[116]
- **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.[117] Based on this limited experience, etanercept is not presently recommended for the treatment of COVID-19.
- **Bruton's tyrosine kinase (BTK) inhibitors**: BTK inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, are FDA-approved for the treatment of certain lymphomas. BTK is involved in macrophage activation, a phenomenon seen in COVID-19 that may play a role in the cytokine hyperinflammatory syndrome through a pathway of toll-like receptors, TLR3, TLR7, and TLR8.[118] When used in an animal model of influenza, BTK inhibitors rescued mice from lethal lung injury.[119] A case series report on patients who developed COVID-19 while receiving ibrutinib for Waldenstrom Macroglobulinemia suggested no worsening in outcome and possibly less of an inflammatory response.[120] Acalabrutinib is being testing in an RCT of non-critically ill patients with COVID-19 (NCT04346199).

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