JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19

Updated June 30, 2020, and replaces the version of June 15, 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? June 30, 2020, Update

- A new recommendation regarding the use of dexamethasone in patients with severe COVID-19, based on preliminary data from the RECOVERY trial.
- Reported drug-drug interaction between remdesivir and hydroxychloroquine.
- FDA revocation of Emergency Use Authorization for oral formulations of chloroquine phosphate and hydroxychloroquine sulfate.

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 (JHHS) who are managing the inpatient care of patients diagnosed with coronavirus disease 2019 (COVID-19). This guidance 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** 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.

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

Box 1: Resources for Johns Hopkins Clinicians

- VTE Prophylaxis for Symptomatic 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
- JHMI Lab Testing Guidance for COVID-19 Inpatients

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 the guidance is updated as needed. The JHHS 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 non-randomized (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 patients at high risk 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, and lymphocytopenia is 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 interleukin-6 (IL-6),[3,4] and nonspecific markers of inflammation including D-dimer, C-reactive protein (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]

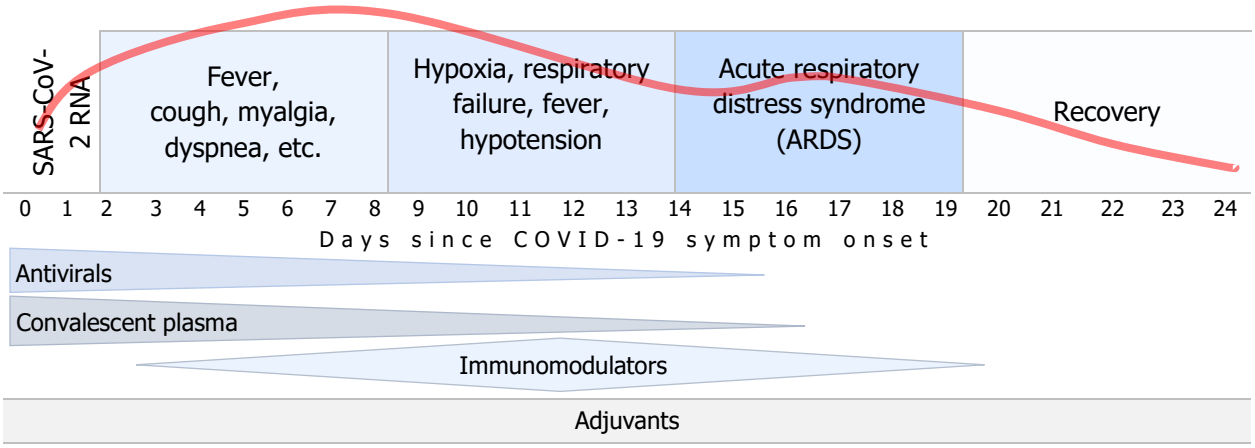
Serum studies in patients with hyperinflammatory syndrome have found increased levels of cytokines, including IL-6, IL-10, IL-2R, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-alpha (TNF-α), that decline as patients recover.[9] Lymphopenia has also been reported, with declines in CD4+ T cells and CD8+ T cells.[9] These cytokine and lymphocyte profiles have some similarities to those seen in chimeric antigen receptor T-cell therapy (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 use of potential therapeutic agents for COVID-19 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, 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 Agents for Antiviral Effect in the Treatment of COVID-19

A. Convalescent Plasma or Serum-Containing Neutralizing Antibodies

Rationale: 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.[18-22] 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. It may also augment innate immunity through complement activation and contribute to antibody-dependent cellular cytotoxicity of infected cells.[22] Convalescent plasma was 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.[23-25] A matched case-control study of 45 adult patients hospitalized in New York reported greater improvement in oxygenation and lower mortality in patients who received convalescent plasma with anti-spike antibody titers ≥1:320 compared to the matched controls.[26] An open-label RCT from China included 103 of 200 planned participants; the trial was stopped early as the pandemic halted enrollment in Wuhan. There were 52 patients randomized to receive convalescent plasma and 51 to receive standard treatment.[27] The primary outcome, clinical improvement within 28 days of treatment based on a 6-point scale, was similar between study arms. Notably, the median duration of symptoms at the time of randomization was 30 days, with 94% of participants in the

convalescent plasma arm having >14 days of symptoms at the time of randomization. This study suggests that late use (after 30 days of symptoms) of convalescent plasma does not improve clinical outcomes.

Benefits and risks: It is believed that convalescent plasma is most likely to be beneficial 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,[22,28,29] allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.[28,29] A review of convalescent plasma therapy for severe or life-threatening COVID-19 in 5,000 patients in the United States found that serious adverse events (SAEs) at 4 hours post-administration occurred in <1% of patients.[30] Among the SAEs reported were 15 deaths (0.3%), with 3 determined to be possibly related and 1 determined to be probably related to the convalescent plasma therapy. A severe allergic transfusion reaction occurred in 3 patients. TACO or TRALI was reported in 18 patients; 2 of those cases were judged to be definitely related to convalescent plasma therapy, 9 as possibly related, and 7 as probably related. This review provides evidence for the safety of convalescent plasma therapy for patients with severe COVID-19.

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 U.S. Food and Drug Administration (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, and its availability is subject to supply. As of this writing, access at JHMI is available through a system-wide expanded access investigational new drug protocol. Clinicians who wish to request convalescent plasma for the treatment of patients in critical care should email 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 the donation of convalescent plasma for use at JHH should email JHUcovidplasma@jhmi.edu.

B. DAS181

DAS181 is not available outside of clinical trials.

DAS181 is a recombinant sialidase fusion protein. It cleaves sialic acid, an important part of viruses binding to cell surfaces in the respiratory tract, potentially decreasing the ability of viruses to enter cells. DAS181 has potential antiviral activity against parainfluenza, metapneumovirus, enterovirus, and influenza. Because coronaviruses also have a sialic acid–binding domain, DAS181 may have activity against SARS-CoV-2.[31] 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.[32] Reported adverse

effects include bronchospasm; dysgeusia; diarrhea; throat irritation; and elevations in alkaline phosphatase, transaminases, creatinine phosphokinase, lactate dehydrogenase, and prothrombin time.

C. Interferon Beta-1b

Interferon beta-1b: Interferon (IFN) beta-1b is known to have an antiviral effect through the upregulation of the immune response, inhibition of mRNA translation (likely), and promotion of viral RNA degradation. It also has immunomodulatory activity and is FDA-approved for relapsing-remitting multiple sclerosis. IFN beta-1b has modest activity in vitro against SARS-CoV-1 and MERS-CoV.[33,34] An open-label RCT of 127 participants compared IFN beta-1b plus ribavirin (RBV) plus lopinavir/ritonavir (LPV/RTV) with LPV/RTV alone in adult patients with <7 days of symptoms and RBV plus LPV/RTV with LPV/RTV alone in patients with 7 to 14 days of symptoms.[35] Patients with <7 days of symptoms who received IFN beta-1b had a shorter time to negative reverse transcription polymerase chain reaction (PCR) results for SARS-CoV-2 and to symptom resolution.[35] It is likely that IFN beta-1b provided most of the clinical benefit observed in this study; however, a placebo-controlled Phase III trial would be helpful to confirm findings.

D. Remdesivir

Remdesivir (RDV) is an intravenous antiviral medication that has in vitro activity against SARS-CoV-2 and other coronaviruses.[36,37] A macaque model treated half of 14 macaques with viral challenge with RDV 12 hours after inoculation.[38] The 7 animals who received RDV did not develop respiratory symptoms and had less or no development of pulmonary infiltrates on radiography. Perhaps the most important finding from this study is that although the viral load (RT-PCR) from upper respiratory and pulmonary specimens did not differ by treatment arm, the infectious viral titer from pulmonary specimens was 100-fold lower 12 hours after RDV administration.

The ACTT-1 clinical trial (double-blind, placebo-controlled; sites in North America, Europe, and Asia) recently reported preliminary, 15-day follow-up results from 1,063 participants with severe COVID-19 pneumonia, defined as infiltrates on imaging or SaO2 <94%: patients who received RDV had a shorter time to recovery (11 days) than patients who received placebo (15 days).[39] Results of that trial also suggested a trend toward reduced mortality among those receiving RDV, with Kaplan-Meier 14-day estimates of 7.1% for the RDV arm and 11.9% for the placebo arm. Subgroup analysis found that patients requiring supplemental oxygen but not mechanical ventilation or extracorporeal membrane oxygenation (ECMO) had reduced time to recovery. There was no difference in outcomes among those who were mechanically ventilated or on ECMO. Further analysis of the study is planned to include 28-day endpoints and virological data.

An RCT of 5- versus 10-day RDV treatment included 397 participants with evidence of pneumonia (pulmonary infiltrates and SaO2 ≤94% on room air or receiving supplemental oxygen) who could not be on mechanical ventilation or ECMO.[40] The study reported no difference in clinical outcomes based on treatment duration arm. On day 14, 60% of patients in the 5-day arm were discharged from the hospital compared to 52% in the 10-day arm, and 8% of the 5-day arm patients compared to 17% of the 10-day arm patients were receiving mechanical ventilation or ECMO. By day 14, 8% in the 5-day arm had died, compared to 11% in the 10-day arm. Patients who received 10-day treatment were more likely to experience SAEs than patients in the 5-day treatment arm (35% compared to 21%) and to discontinue treatment due to adverse events (10% compared to 4%).

A clinical trial from China randomized a much smaller number of participants (237) to RDV or placebo. This study ended early due to the waning of the epidemic in China. No difference by arm was observed in clinical resolution.[41]

On May 1, 2020, based on the preliminary results from the ACTT-1 and the 5-day versus 10-day RDV study noted above, the FDA issued an emergency use authorization (EUA) for RDV for the treatment of COVID-19.[42] This EUA does not imply FDA approval of RDV for treatment of COVID-19, and RDV remains an investigational drug.

Who is likely to benefit from RDV treatment? The ACTT-1 study reported no significant difference in RDV effect among study participants who entered with ≤10 days or >10 days of symptoms. The RCT from China reported a trend toward improved outcome among patients with shorter duration of symptoms (<10 days), and the 5-day versus 10-day RDV treatment study reported that 62% of participants with <10 days of symptoms at the time of first RDV dose were discharged from the hospital compared to 49% of those with ≥10 days of symptoms. Taken together, these data and the proposed mechanism of RDV action (inhibition of viral replication) suggest that RDV is likely to be most useful when given to patients earlier in the course of COVID-19 disease, possibly within the first 10 days of symptoms).

The ACTT-1 study found no difference in the primary outcome of median time to recovery among participants on mechanical ventilation or ECMO (rate ratios 0.95; 95% confidence interval 0.64-1.42). Subgroup analysis based on oxygen requirement at enrollment found the greatest 14-day mortality difference in the group requiring supplemental O2 via nasal cannula (95% confidence interval). Kaplan-Meier 14-day mortality estimates by subgroup found that the number needed to treat to prevent 1 death is as follows:

Table: Number Needed to Treat to Prevent 1 Death by Patient Condition at Enrollment[39]

Illness Score at Enrollment (ACTT-1 category assignment)	**Number Needed to Treat to Prevent 1 Death**
4: No supplemental oxygen needed	100 (no difference in mortality)
5: Supplemental oxygen via nasal cannula	12
6: High flow O2 or non-invasive ventilation	Favored placebo
7: Invasive mechanical ventilation or ECMO	36

Based on the evidence that is currently available, it appears that the COVID-19 patients most likely to benefit from RDV treatment are those who need supplemental oxygen but not mechanical ventilation or ECMO.

Side effects and adverse events: Although the full range of RDV side effects may not yet be known, potential side effects need to be weighed against potential benefits when making treatment decisions. In the 5-day versus 10-day RDV treatment study, SAEs were reported in 21% of patients in the 5-day group and 35% in the 10-day group; adverse events leading to discontinuation of RDV were reported in 4% (5-day) and 10% (10-day group).

Common adverse events (from RDV or the underlying disease) reported in clinical trials[39,40] include acute respiratory failure, anemia, gastrointestinal (constipation, nausea, vomiting, diarrhea), hypoalbuminemia, hypokalemia, increased bilirubin, infusion-related reactions (hypotension, nausea, vomiting, diaphoresis, shivering), and thrombocytopenia.

Rare or occasional side effects reported in clinical trials[39,40] include hypoglycemia, insomnia, elevated prothrombin time (without a change in INR), pyrexia, rash, and transaminase elevation.

Optimal treatment duration: The optimal RDV treatment duration is unclear. Ten days of treatment were studied in both the ACTT-1 RCT and the RCT from China.[41] The 5-day vs. 10-day RDV treatment study found no significant difference in effectiveness between the 2 duration groups. The 5-day treatment arm did have a higher proportion of patients discharged from the hospital and a higher proportion of patients with an improved symptom scale by day 14. The 10-day arm had more SAEs (35% versus 21% of patients), some of which may have been due to RDV. Given the lack of data suggesting a clear benefit and the increase in adverse events with >5 days of RDV, and given the current limited supply of RDV, it appears that a 5-day course of RDV treatment is the most reasonable approach.

Dosing: See Remdesivir Dosing Guidance Under EUA and Allocation Criteria (Appendix B).

Drug-drug interactions: RDV is a substrate for CYP2C8, CYP2D6, CYP3A4, and OATP1B1 and an inhibitor of CYP2A4, OATP1B1, and OATP1B3. The antagonism that occurs between hydroxychloroquine (HCQ) and RDV led the FDA to recommend against concomitant use of RDV and HCQ or chloroquine phosphate in a letter issued on June 15, 2020. HCQ has a long half-life, so a patient who takes the medication for any indication along with RDV is less likely to experience a clinical benefit from RDV, even several days after discontinuing HCQ.

Considerations for use with impaired kidney function: RDV is eliminated primarily (49%) in the urine as an active metabolite, GS-441524, and only 10% as RDV (see FDA Fact Sheet for Health Care Providers Emergency Use Authorization [EUA] of Remdesivir [GS-5734™]). Clinical trials of COVID-19 treatment have excluded patients with an eGFR <30 mL/min/m^2 or who are on renal replacement therapy. Concerns with use in patients with kidney impairment include the lack of data on the pharmacokinetics of remdesivir in this population and that remdesivir contains excipient sulfobutylether-β-cyclodextrin sodium salt (SBECD). SBECD is cleared by the kidneys and may accumulate in patients with decreased kidney function. The FDA does not recommend the use of RDV in patients with eGFR <30 mL/min/m2 unless the potential benefit outweighs the potential risk (see FDA fact sheet). However, intravenous voriconazole also contains SBECD, and it has been extensively used and evaluated in patients with varying degrees, including severe, kidney impairment. There has been no increased risk in renal or hepatic toxicity observed in several reports when IV voriconazole was used in patients with eGFR <50 and eGFR <30 mL/min/m2 or those receiving renal replacement therapy.[43-48]

Treatment monitoring: Clinicians should monitor patients who are receiving RDV treatment as follows:

- **Alanine transaminase (ALT) and aspartate aminotransferase (AST) daily:** If the ALT or AST rises to >5x the upper limit of normal (ULN) or the patient develops symptoms of drug-induced liver injury, RDV should be discontinued and should not be restarted during the hospital admission.
- **Creatinine daily:** In addition to evaluating for causes of acute kidney injury, clinicians should discontinue RDV if there is a decline ≥50% in eGFR if RDV is the most likely cause.

Box 2: JHHS Formulary Restriction Status for Remdesivir

Clinicians should evaluate patient eligibility and interest in participating in available remdesivir clinical trials. Clinical trials are the preferred mechanism for patient access to RDV. If a clinical trial is not a viable option for a patient, the clinician can request RDV if the patient meets the following criteria:

- Meet remdesivir EUA criteria (see FDA Fact Sheet for Health Care Providers Emergency Use Authorization [EUA] of Remdesivir [GS-5734™]).
- COVID-19 positive confirmed during the current episode of care.

Box 2: JHHS Formulary Restriction Status for Remdesivir

- Hospitalized for less than 10 days.
- ALT <5 times ULN to initiate and continue RDV. Remdesivir should be stopped if there are signs or symptoms indicating hepatotoxicity.

All initial courses are restricted to 5 days of treatment. For patients who are intubated, the care provider may request an additional 5-day course if a patient has not improved on current therapy.

E. Agents With Speculative Antiviral Effect Against COVID-19

Box 3: Recommendation for Agents to Avoid as Treatment for COVID-19 Specifically

☑ Because there is no or inadequate 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, except in a clinical trial.

- 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)
  - Hydroxychloroquine (HCQ)*
  - 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

*Use of HCQ for treatment or prophylaxis of COVID-19 is prohibited at JHHS unless it is part of a clinical trial. Patients who may have been prescribed HCQ for prophylaxis as an outpatient should not continue therapy for prophylaxis as an inpatient unless part of a clinical trial.

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.[49] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression,[50] leading to concerns of a theoretical risk with the use of ACE inhibitors or ARBs.

At present, no clinical data have indicated 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.[51] The best evidence suggests similar or improved outcomes among people on chronic ACE or ARB therapy who develop COVID-19.[52]

There is no need to discontinue ACE inhibitor or ARB therapy in patients diagnosed with COVID-19; it is appropriate to follow existing clinical recommendations for discontinuation of treatment with ACE inhibitors or ARBs when appropriate.

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.[53] A subsequent study reported no increase in viral clearance with HCQ plus azithromycin.[54] Data suggest no benefit and potential harm with the use of HCQ plus azithromycin. A retrospective study of patients who did not have COVID-19 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.[55] No clinical efficacy was found in a study of azithromycin against MERS-CoV.[56]

Baloxavir marboxil: Baloxavir marboxil 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 marboxil as an agent against SARS-CoV-2.

Darunavir/ritonavir (DRV/RTV): An in vitro study of DRV/RTV and remdesivir against SARS-CoV-2 reported no activity for DRV/RTV compared to potent activity for remdesivir.[57] 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.[57]

Famotidine: Famotidine is hypothesized to bind to SARS-CoV-2 papain-like protease and inhibit replication. Unpublished anecdotes have suggested possible value of this agent in treating COVID-19, and a trial of high-dose intravenous famotidine for COVID-19 is underway.[58]

Favipiravir: This inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.[59,60] An open-label, non-randomized 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 findings.[60] An RCT comparing favipiravir with umifenovir (brand name Arbidol; a fusion inhibitor approved for use to treat 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.[59] This drug is not approved by the FDA and is not available in the United States.

Hydroxychloroquine (HCQ): Although HCQ has in vitro activity against SARS-CoV-2 and some other viruses,[61,62] it has not translated into efficacy in the treatment of any viral infection. Notable studies have reported failure in animal models for Ebola virus and failure in human trials for influenza and HIV.[63-65] A retrospective study in France 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.[53] 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.[66] In another study from France, viral clearance was measured in 11 patients treated with HCQ plus azithromycin. Of the 9 patients who remained under observation on day 5 or 6, 80% still had positive PCR test results.[54] In an RCT from China that included 30 patients, 86% of those treated with HCQ and 93% of controls had cleared viral

shedding at day 7.[67] In a larger, open-label RCT from China that included 150 patients, negative PCR test results at day 28 were reported in 85% of those who received HCQ and in 81% of those who did not receive HCQ (seroconversion was similar between groups at days 4, 7, 10, 14, and 21 as well).[68]

An open-label RCT from China evaluated 62 patients with mild illness who were randomized to receive HCQ or usual care.[69] Fever resolved more rapidly (2.2 days vs. 3.2 days), and there was greater radiographic improvement in pneumonia (81% vs. 55%; *P*=.05) in the HCQ group. The value of these results is limited by the quality of the study endpoints and open-label design. 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.[70] A retrospective study of HCQ use across the United States Veterans Health Administration system reported on 368 patients who received HCQ, HCQ plus azithromycin, or neither.[71] Patients who received only HCQ had the highest rate of mortality; mortality was lower and similar among 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. Retrospective studies from New York State and multinational sites have reported similar findings of no convincing benefit from HCQ when used to treat patients with COVID-19.[72-74] Mortality may have been increased with HCQ; however, study limitations prevent making any strong conclusions regarding harm. On March 28, 2020, the FDA issued an EUA for use of HCQ to treat COVID-19. This EUA was revoked on June 15, 2020, in response to increasing evidence (including from RCTs) that HCQ has no effect against COVID-19.[75] Multiple RCTs, including those sponsored by the NIH, have been halted because of the futility of HCQ treatment or under-enrollment.[76]

Indomethacin or other NSAIDs: Indomethacin (INDO) has been suggested as a possible therapeutic agent for COVID-19, 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.[77] 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 published in *The Lancet* 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.[78] 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.[79]

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).[80] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[81] A non-randomized 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.[82] A small clinical trial that randomized 86 patients with mild COVID-19 to 1 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.[83]

Nitazoxanide: This agent has been tested in vitro against MERS-CoV and SARS-CoV-2 and found to have activity.[84] 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.[85]

Umifenovir: This agent was routinely used in China to treat patients with COVID-19.[86] There are no data to support its effectiveness. This drug is not approved by the FDA and is not available in the United States.

RBV: In a systematic review, RBV was not found to be beneficial against SARS-CoV-1.[87] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[88]

Vitamin C: Vitamin C has been suggested as a treatment option for COVID-19. This is based on a prospective randomized trial of intravenous vitamin C in patients with sepsis and acute respiratory distress syndrome.[89] 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.[90]

IV. Use of Immunomodulators to Treat COVID-19

Box 4: Recommendations for the Use of Immune Modulatory Agents to Treat COVID-19

☑ **Corticosteroids:** Clinicians should not prescribe dexamethasone or other steroids for the management of COVID-19 among patients with a room air SaO2≥94%.

- **Dexamethasone:** Clinicians should prescribe dexamethasone for the treatment of COVID-19 only to the following patients:
- Those who have >7 days of COVID-19-related symptoms AND either a persistent need for non-invasive supplemental oxygen to maintain SaO2≥94% or who require mechanical ventilation.
- **Dosing:** Dexamethasone should be dosed as 6 mg IV or by mouth once daily for up to 10 days; it should be discontinued at the time of hospital discharge if less than a 10 day course has been completed.
- **Use in pregnancy:** Because dexamethasone readily crosses the placenta,[91,92] the agents recommended for pregnant patients are prednisolone 40 mg IV daily or hydrocortisone 80 mg by mouth twice daily. Both of these medications have lower fetal concentrations as a result of either limited placental crossing (prednisolone) or rapid placental metabolism (hydrocortisone).

  This recommendation is based on the RECOVERY RCT, a multicenter open-label trial that compared several arms, including a dexamethasone arm, to standard care in the United Kingdom.[93] In this study there was a 35% reduction in mortality with dexamethasone among the sub-group receiving mechanical ventilation. There was also a reduction in mortality among those receiving supplemental

Box 4: Recommendations for the Use of Immune Modulatory Agents to Treat COVID-19

oxygen and a trend toward increased mortality among the sub-group not receiving supplemental oxygen.

☑ **mAbs:** Tocilizumab is the preferred mAb; however, robust clinical trial data to support its use is lacking; 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 x 1 dose.[94-96]
  - 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.[94]
- 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.
- Antimicrobial prophylaxis should be continued in patients who are taking them for immunodeficiency conditions.
- 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.

☑ **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 coenzyme A (HMG-CoA) reductase inhibitors (statins)
- TNF-α inhibitors

*Alternative: Siltuximab (supply based on availability) is administered as 11 mg/kg intravenously x 1 dose.[97] The dose should be rounded to the nearest vial size in consultation with the pharmacy, and the maximum dose should not exceed 1100 mg.

A. Corticosteroids

The new recommendation for the use of dexamethasone (added in the 6/30/2020 update) is based on preliminary findings from the RECOVERY trial and results from earlier studies of corticosteroid treatment for viral pneumonia. Critical findings from this study are that dexamethasone benefit was greatest among those who were most severely ill (mechanical ventilation) and only after an initial phase of symptoms. This study is as yet unpublished; the comparison presented in the study pre-print compared groups who had symptoms for ≤7 days

and >7 days. Notably, the patients who benefited most had >10 days of symptoms; using a >10-day criteria for the use of dexamethasone may be reasonable.

Note: Because the RECOVERY trial specifically used dexamethasone, the recommendations here are for the use of dexamethasone rather than any alternative corticosteroid such as methylprednisolone.

RECOVERY trial: This unblinded open-label, multi-site, multi-arm RCT conducted in the United Kingdom included a dexamethasone treatment arm. In this study, all patients hospitalized with COVID-19 were eligible to participate unless the attending clinician determined that participation would be inappropriate.[93,98] The 2,104 patients who were randomized to the dexamethasone arm received 6 mg by mouth (P.O.) or IV daily for up to 10 days. Those who required mechanical ventilation at the time of randomization had a median of 13 days of symptoms. Patients who were receiving non-invasive oxygen had a median of 9 days of symptoms, and those who were not receiving supplemental oxygen had a median of 6 days of symptoms. When their results were compared to those of 4,321 patients who received standard care, the rate ratio of mortality at 28 days was 0.65 (p=0.0003) for patients on mechanical ventilation, 0.8 (p=0.002) for patients receiving non-invasive supplemental oxygen, and 1.22 (p=0.1; a statistically non-significant increase in mortality) for patients who were not receiving supplemental oxygen. The benefit was reported only for patients who had >7 days of COVID-19-related symptoms. In patients with ≤7 days of symptoms, neither benefit nor harm was associated with dexamethasone treatment, though there was a trend toward increased mortality.

The findings from the RECOVERY trial may not be generalizable to corticosteroid use overall for treatment of COVID-19. Dexamethasone has minimal mineralocorticoid activity, leading to less of an effect on the sodium balance and potentially causing fewer problems with fluid retention, which is a common complication of viral pneumonitis/ARDS. Thus, at present, dexamethasone is the preferred glucocorticoid for treatment of non-pregnant patients. As noted above, to achieve lower fetal glucocorticoid concentrations, prednisolone or hydrocortisone are reasonable alternatives for pregnancy.

Despite the multi-arm, open-label design of the trial, the use of a 28-day mortality endpoint and large enrollment makes this finding important. The study does have several limitations for direct comparison to the current epidemic in the United States. Most notably, the mortality rate in this study was higher than what has been reported in the U.S.[99] In addition, the use of 28 day-mortality endpoint may obscure later complications, such as secondary infections, related to dexamethasone.

The GLUCOCOVID trial (pre-print), a small open-label study that included 85 patients, compared results in patients prescribed a glucocorticoid (methylprednisolone) with a group of patients randomized to receive either glucocorticoid or no glucocorticoid. [100] Patients included in the analysis had to have ≥7 days of COVID-19 symptoms, pneumonia, hypoxia, elevated inflammatory markers, and not be receiving mechanical ventilation. Methylprednisolone was dosed as 40 mg every 12 hours for 3 days, then as 20 mg every 12 hours for 3 days. In the unadjusted intention-to-treat analysis, a composite score of death/ICU admission/non-invasive ventilation found no significant difference by methylprednisolone use. In adjusting for age, methylprednisolone prescription was associated with a 24% reduction in the relative risk of the composite endpoint. Very importantly, the only component of the composite endpoint that differed by methylprednisolone was ICU admission. Death was similar: 20% in the methylprednisolone recipients and 18% in those who did not receive methylprednisolone. The lack of a randomized design and the primary benefit appearing to be delayed or reduced ICU transfer are substantial limitations of this study.

Studies of corticosteroids in other viral pneumonias have generally shown no benefit or harm. An earlier RCT of corticosteroids for the treatment of (non-COVID-19) pediatric bronchiolitis that was likely predominantly viral in origin, found either no clinical benefit or notable harm.[101] A meta-analysis of 10 observational studies of

corticosteroid use for influenza found that these agents may increase the risk of mortality.[102] Several published observational studies of corticosteroid use in the treatment of SARS-CoV-1 have reported adverse effects and no benefit.[103] A retrospective study from China compared 26 patients with COVID-19 who received methylprednisolone to 20 patients who did not; all patients had relatively mild disease. The authors reported no clear benefits or harms associated with methylprednisolone use.[104] A study from a multi-hospital health system in Michigan compared outcomes in patients who were admitted for COVID-19 treatment before or after the adoption of a protocol for early corticosteroid treatment.[105] Although the results suggest benefit, this study had multiple limitations, including the pre-/post-design set in a landscape of rapidly expanding clinical knowledge and medical practice-changing in real-time.

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

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

Box 5: 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 – Black race – Solid organ transplant recipient – Stem cell transplant within the previous 12 months – Cardiac disease – Diabetes – Obesity (body mass index >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

Box 5: Criteria for Consideration of COVID-19 Treatment with IL-6R or IL-6 Antibodies

- **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.

Tocilizumab: Tocilizumab is an IL-6 receptor blocker that is FDA-approved for the treatment of CAR-T–associated CRS. Because COVID-19–associated hyperinflammation is similar to CAR-T–associated CRS, it is plausible that tocilizumab, which is widely used to treat CAR-T–associated CRS, might be beneficial in the treatment of COVID-19. This also suggests that IL-6 may play a role in COVID-19. To date, though, the clinical evidence of benefit of immune modulatory therapy for patients with COVID-19 is limited. A case series from China reported a striking and rapid improvement in oxygen requirement in the majority of 21 patients treated with tocilizumab.[15] Another case series reported on 301 patients in Italy who were prescribed tocilizumab, with no reported increase in adverse events.[106] This study has substantial limitations, including the complexity of the analysis and the numbers of patients who either did not receive tocilizumab after it was prescribed or who experienced delayed administration. These case series used 8 mg/kg dosing of tocilizumab, which is supported by data on rapid clearance of tocilizumab during CRS, the standard dose for CAR-T–associated CRS,[95] and the concentration-dependent half-life.[94] Additional case series have supported the overall safety of this agent.[107]

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.[97] 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 is another IL-6 inhibitor under investigation for use in COVID-19.

Lenzilumab neutralizes human GM-CSF. In vitro data suggest it may limit CRS. Given the role of GM-CSF in inflammation and COVID-19,[17] lenzilumab may 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.[108] Long-term use of such mAbs increases the risk of bacterial, mycobacterial, and fungal infections and reactivation of herpes simplex and herpes zoster.[108] 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.[109-111] However, there may be a risk of worsening of bacterial infections with short-term use.[112] Patients with known and not yet controlled

infection (e.g., bacteremia) should not receive mAbs until the bacterial infection is controlled. Patients who are taking antimicrobial prophylaxis should continue to do so, and it may be reasonable for patients who recently stopped taking antimicrobial prophylaxis to restart the medications.

The following adverse effects have been reported:[108]

- 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. 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.[113] IVIG has been used in the treatment of multiple conditions, including SARS and COVID-19, to control pathogenic inflammation. [114] A case series of 3 patients reported on the use of IVIG at the point of clinical deterioration and presumed shift to cytokine dysregulation.[115] 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 determine whether IVIG has a therapeutic role in COVID-19.

D. 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.

JAK inhibitors: 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.[116] 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,[11] anakinra has been used off-label for the treatment of COVID-19. A retrospective cohort study from Italy found that 3 of 29 (10%) patients who received anakinra died, compared with 7 of 16 (44%) patients who did not receive anakinra.[117]

HMG-CoA reductase inhibitors (statins): In addition to altering cholesterol synthesis, these agents have an anti-inflammatory role. Statins may modify SARS-CoV-2–mediated inflammation.[118]

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.[119] Based on this limited experience, etanercept is not presently recommended for the treatment of COVID-19.

Bruton 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 the toll-like receptors (TLRs) TLR3, TLR7, and TLR8.[120] When used in an animal model of influenza, BTK inhibitors rescued mice from lethal lung injury.[121] 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.[122] A case series of 19 patients with COVID-19 treated with acalabrutinib suggested overall safety and a reduction in inflammatory markers.[123]

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Appendix A: Johns Hopkins Medicine Remdesivir Patient Information

Johns Hopkins Scarce Resources Group

JOHNS HOPKINS MEDICINE

REMDESIVIR

You may be eligible to receive a new investigational drug called remdesivir to treat the symptoms of COVID-19. You are receiving this information because your physician is considering this medicine for you.

About Remdesivir
Remdesivir is an intravenous (IV) medication, which means it is given into your vein. The Food and Drug Administration (FDA) has allowed remdesivir for emergency use for a limited group of patients with COVID-19. This drug has been shown to work against some viruses, including COVID-19. Remdesivir is still called investigational because it is still being studied. There is limited information known about the safety and effectiveness of using remdesivir to treat people in the hospital with COVID-19.

A Limited Supply
The federal and state governments have sent a limited supply of remdesivir to some Maryland and Washington DC hospitals. If we have adequate supply on hand for all patients, remdesivir will be provided to you if your physician prescribes it. When the demand is greater than the supply, a team at the hospital will oversee the process to determine who receives the medication. This team is different from your care team. We are doing everything we can to make this a fair and equitable process for all patients.

Determining Who Receives Remdesivir
If the demand is greater than supply, the hospital will use the same criteria for all patients when making difficult decisions about giving remdesivir. The criteria include the following:

- lab test confirmation of COVID-19
- length of time you have been in the hospital
- how your recovery is going

Based on these criteria, we will put patients into priority groupings. For patients in the highest priority group, we will use a process that chooses at random which patients will receive remdesivir. If there is still medication on hand, we will then run the same process for those in lower priority groups, until all of the drug has been dispensed.

Taking Remdesivir
According to the FDA, the optimal length of treatment is not known. If you are chosen to receive this medicine, a 5-day course of treatment will be reserved for you. We will monitor you daily for any side effects. You will receive the full 5-day course unless you have a significant side effect that requires stopping the medication, you are well enough to be discharged from the hospital, or you choose to stop it. By providing a 5-day course of treatment (instead of 10 days), the maximum number of patients will have a chance to receive and benefit from remdesivir. Some patients on a ventilator may qualify for an additional 5-day course.

For more details, we have provided you with a fact sheet about the medication. Please read it.

Your physician will also speak with you about the benefits and risks of remdesivir as well as alternative treatments.

Questions
Our care teams are committed to providing you with exceptional, compassionate care. Please do not hesitate to speak with any member of your care team if you have any questions.

Appendix B: COVID-19 Pandemic: Remdesivir Allocation Plan

Johns Hopkins Scarce Resources Group

This is a dynamic document subject to frequent updates

Current version: May 29, 2020

May 29, 2020

COVID-19 Pandemic: Remdesivir Allocation Plan

1. Try to maintain a sufficient supply of remdesivir to meet demand

2. Remdesivir available to only those patients:
enrolled in an IRB-approved clinical trial, on compassionate use protocol, or meet EUA criteria

Clinical Trial

3. Anticipate that trials will provide their own remdesivir supply, if the trial uses it

(For example, ACTT-2 will have its own supply of remdesivir)

Expanded Access / Compassionate Use

3. Gilead has been supplying the drug (separate from EUA supply)

Per Gilead, expanded access available for Peds or Pregnancy and may be phased out soon

The course and dosing of remdesivir provided through this channel should follow the expanded access protocol and NOT limited by any EUA allocation process

Emergency Use Authorization

3.
- **EUA criteria:**
  - Adults and children with suspected or lab-confirmed COVID-19; AND
  - SpO2 ≤94% on room air, requiring supplemental oxygen, mechanical ventilation, or ECMO
- Given the current supply situation, for all patients <u>prescribed</u> remdesivir, administer no more than a total 5-day course. The only exception is for patients on a vent (w/ or w/o ECMO) at the time of completing first course: If their attending wishes to order another 5-day course on Day #6, the patient is eligible to go back into the allocation process for another 5-day course once, on Day #6 only.
- If we have supply on hand, we will not reserve any supply for future patients that may come in.
- If demand exceeds supply on a given day, follow tiered allocation system as below (Tier 1 patients with first priority for distribution)

Allocation Process

- All initial courses are limited to 5 days for all patients (whether or not on a vent or ECMO), regardless of their clinical status (Per the FDA, the optimal duration of treatment for COVID-19 is unknown). As above, there can be one request for a second course for vented patients
- Once started, a 5-day course will not be stopped to make drug available for another patient

4.

<u>Tier 1 Patients</u>

- Meet EUA criteria

AND all 4 of the below:

- Confirmed COVID-19 (RNA-positive respiratory sample)
- In hospital ≤7 days (during this hospitalization) (earlier initiation of treatment is thought to provide the best chance at improvement)
- No evidence of clinical improvement (patients can be eligible immediately upon admission)
- Do not meet any Tier 3 criteria

<u>Tier 2 Patients</u>

Meet EUA criteria AND are not in Tier 1 or Tier 3

<u>Tier 3 Patients</u>

- Meet EUA criteria

BUT also meet ANY of the criteria below:

- Requiring significant and more than 1 medication for vasopressor or inotropic support; or
- On ECMO

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NOTES

The allocation process may change over time

1. We will modify this protocol as more data become available

Random Selection

1. When remdesivir demand exceeds supply, the available supply will be allocated to patients based on a random selection every morning. Tier 1 random selection will take place first. If after all Tier 1 patients have been allocated remdesivir, then a random selection would follow for Tier 2 patients, and then Tier 3, as supplies allow.
2. All patients eligible for the random selection process will have only one "entry" in the random selection each day. There are no additional entries for time waiting for the drug.
3. The patient's tier status (by the patient's clinical team) is determined each morning of the random selection. For example, if a patient enters the random selection on Day #6 of hospitalization, but does not win the random selection on Day 6 or 7, the patient will move to Tier 2 on Day 8 by virtue of now being in the hospital > 7 days.
4. If a compassionate use IND (expanded access) program is NOT in place at the hospital, pregnant women will get first priority within their tier (i.e., they will be first for allocation before the random selection for the others—and if more pregnant woman than supply, a random selection within that group). For pregnancies where a fetal heart rate can be evaluated, it must be present and be consistent with a healthy fetus. To increase supply, hospitals will explore ensuring that expanded access protocols for pregnant women are in place as long as the manufacturer keeps them available. They will do the same for pediatric patients (however, no priority provided for children within the tier their clinical condition dictates).

Supply

1. At present, all allocation decisions will be made at the hospital entity level. As more information and supply comes in, hospitals will explore moving drug to meet demand within and across systems.

Identification of Patients Meeting EUA Criteria

1. Each hospital will determine how to identify patients that meet EUA criteria for remdesivir and whether the attending physician wishes to prescribe it.

Important Instructions for Health Care Providers

We will ask health care providers to communicate to patients or surrogate decision-makers information consistent with the "Fact Sheet for Patients and Parents/Caregivers" (See Link: https://www.gilead.com/remdesivir) prior to the patient receiving remdesivir, including:

- FDA has authorized the emergency use of remdesivir, which is not an FDA approved drug.
- The patient or surrogate decision-maker has the option to accept or refuse remdesivir.
- The significant known and potential risks and benefits of remdesivir, and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives.
- Provider should document that the patient received the EUA Fact Sheet about remdesivir

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Remdesivir Dosing Guidance Under EUA and Allocation Criteria

Patient Age/Weight	EUA Dosing Recommendation	Dosing Under Allocation System when Demand Greater than Supply
Adults and Pediatric Patients weighing greater than or equal to 40 kg *requiring mechanical ventilation or ECMO*	200 mg IV x 1 on day 1 followed by 100 mg IV daily x 9 days, for a total 10-day course	200 mg IV x 1 on day 1 followed by 100 mg IV daily x 4 days, for a total 5-day course *For patients on a ventilator at the end of the 5-day course, an additional 5-day course (100 mg IV daily) may be requested.
Adult and Pediatric Patients weighing >/= 40 kg *NOT requiring mechanical ventilation or ECMO*	200 mg IV x1 on day 1 followed by 100 mg IV daily x 4 days, for a total of 5 days; If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total of 10 days	200 mg IV x 1 on day 1 followed by 100 mg IV daily x 4 days, for a total 5-day course
Pediatric Patients between 3.5 kg to 40 kg *requiring mechanical ventilation or ECMO*	5 mg/kg IV x1 on day 1 followed by 2.5 mg/kg IV daily x 9 days for a total 10-day course	5 mg/kg IV x1 on day 1 followed by 2.5 mg/kg IV daily x 4 days for a total 5-day course *For patients on a ventilator at the end of the 5-day course, an additional 5-day course (100 mg IV daily) may be requested.
Pediatric Patients between 3.5 kg to 40 kg *NOT requiring mechanical ventilation or ECMO*	5 mg/kg IV x1 on day 1 followed by 2.5 mg/kg IV daily x 4 days, for a total of 5 days; If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total 10-day course	5 mg/kg IV x1 on day 1 followed by 2.5 mg/kg IV daily x 4 days for a total 5-day course

Once started, a complete (5 or 10 day) course should be administered unless adverse events require discontinuation, or the patient is discharged to another facility that does not have remdesivir available.