

JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19

Updated September 9, 2020, and replaces the version of August 19, 2020; COVID-19 Treatment Guidance Writing Group of Johns Hopkins University and The Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

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WHAT'S NEW? September 9, 2020, Update

- **Additions regarding convalescent plasma:** New study data, emphasis on early administration for effectiveness, and information about the August 23, 2020, U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA).
- **Remdesivir:** Following the [8/28/20 expanded EUA by the FDA](#), the JHU COVID-19 Treatment Guidance Writing Group does not recommend the use of this antiviral for hospitalized patients who do not require supplemental oxygen [see [Box 2](#) for details].
- **Corticosteroids:** Results from the World Health Organization (WHO) meta-analysis reported.
- **Hydroxychloroquine (HCQ):** This committee now recommends against off-label use of HCQ for the treatment of COVID-19.
- **Appendix B added:** Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families.

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

- **Chair:** Paul G. Auwaerter, MD, MBA, Clinical Director, Division of Infectious Diseases; Professor of Medicine
- **Lead author:** Christopher J. Hoffmann, MD, MPH, Associate Professor of Medicine, Department of Medicine, Division of Infectious Diseases
- **Co-author, [Use of Immunomodulators to Treat COVID-19](#):** Tania Jain, MBBS, Assistant Professor, Department of Oncology, Division of Hematological Malignancies and Bone Marrow Transplantation
- **Contributing members:**
 - Edina Avdic, PharmD, MBA, Associate Director, Adult Antimicrobial Stewardship Program; Program Director, Infectious Diseases Pharmacy Specialty Residency
 - Robin K. Avery, MD, Professor of Medicine
 - Richard F. Ambinder, MD, PhD, Director, Division of Hematologic Malignancies; Professor of Oncology
 - Andrew M. Cameron, MD, PhD, Chief, Division of Transplantation; Professor of Surgery
 - Larry W. Chang, MD, MPH, Associate Professor of Medicine, Department of Medicine, Division of Infectious Diseases
 - Natasha M. Chida, MD, MSPH, Associate Director, Infectious Diseases Fellowship Program; Assistant Professor of Medicine
 - Franco R. D'Alessio, MD, Assistant Professor of Medicine, Pulmonary and Critical Care Medicine
 - Brian T. Garibaldi, MD, Director, Johns Hopkins Biocontainment Unit; Associate Professor of Medicine
 - Elisa Ignatius, MD, MSc, Third Year Fellow, Infectious Diseases, Clinical Pharmacology
 - Tania Jain, MBBS, Assistant Professor of Oncology
 - Andrew Karaba, MD, PhD, Third Year Fellow Infectious Diseases
 - Kieren Marr, MD, MBA, Director, Transplant and Oncology Infectious Diseases; Vice-Chair for Innovation in Healthcare Implementation, DOM; Professor of Medicine
 - Christian A. Merlo, MD, MPH, Director of Outpatient Clinical Operations, Associate Professor of Medicine
 - Pali D. Shah, MD, Medical Director, Johns Hopkins Lung Transplantation; Assistant Professor of Medicine
 - R. Scott Stephens, MD, Director, Oncology and Bone Marrow Transplant Critical Care; Assistant Professor of Medicine

- David J. Sullivan Jr, MD, Professor, Molecular Microbiology and Immunology; Joint appointment in Medicine
- Ethel D. Weld, MD, PhD, Assistant Professor of Medicine, Pharmacology, and Molecular Sciences; Clinical Pharmacology, Infectious Diseases

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, and when available, randomized, controlled clinical trials (RCTs):** The body of available clinical data is growing, but remains suboptimal to support recommendations for the use of any specific pharmacologic treatment for COVID-19. Much of the existing data are drawn from non-randomized studies. RCTs with strong study design and adequate sample size provide the best possible data on which to base specific recommendations.
- **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 patient 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

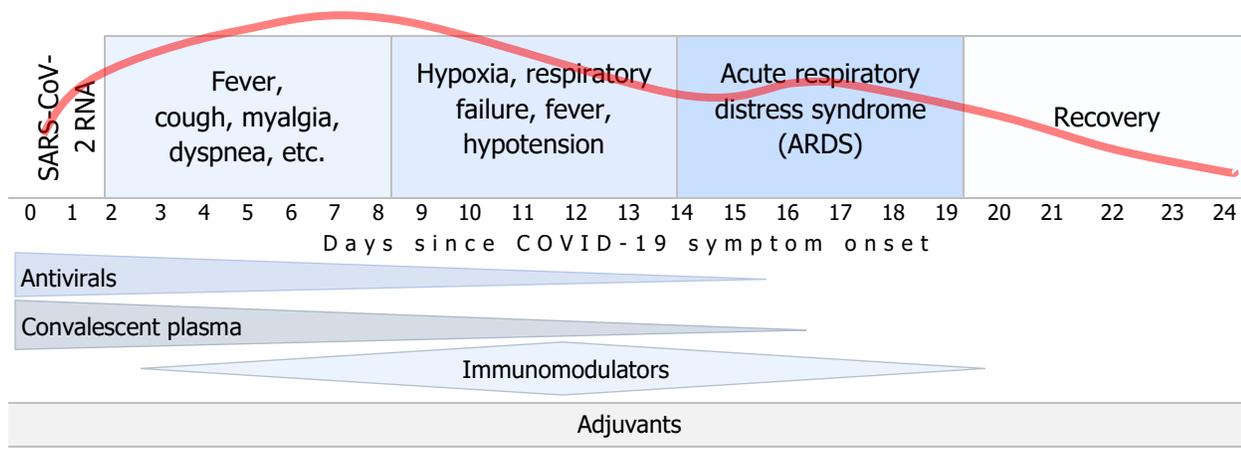
protein (CRP), and ferritin. Patients may progress to multiorgan failure as a result of the cytokine-mediated hyperinflammation or uncontrolled viral infection.⁵ Microvascular thrombosis and venous thromboembolism have also been reported and may be a separate or related pathway to respiratory compromise.⁶⁻⁸

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 cytokine 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 the use of potential therapeutic agents for COVID-19 is, largely, insufficiently understood. 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 To be most effective, convalescent plasma should be administered as soon after infection as possible.

Available data: Convalescent plasma was used in China and has been used more extensively in the United States for the treatment of COVID-19. An open-label RCT from China that was conducted from mid-February through April 1, 2020, included 103 of 200 planned participants; the trial was stopped early as daily cases quickly waned in Wuhan. There were 52 patients randomized to receive convalescent plasma and 51 to receive standard treatment.²³ 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, suggesting that late use of convalescent plasma does not have a substantial benefit. A study from the Netherlands was halted early after a safety review reported no difference in mortality or time to clinical improvement by study arm among 86 participants.²⁴ At the time of enrollment, participants had experienced a median of 10 days of symptoms, and most had high levels of neutralizing antibodies, which may explain the reported similar overall outcomes between treatment and control groups. The results of these 2 RCTs, both terminated early, suggest that use of convalescent plasma after 10 days of symptoms does not improve clinical outcomes. Several reported matched case series have reported promising results.²⁵⁻²⁹

Analyses of the use of convalescent plasma administered through the open-label U.S. FDA expanded access program (EAP) indicated overall relative safety (though not compared to placebo) and suggested reduced mortality with transfusion soon after diagnosis compared to >4 days after diagnosis and use of higher titer units. The safety study identified a low risk of adverse events among 21,987 patients (see below). A mortality analysis included 35,322 patients with severe COVID-19 who were transfused between April 4 and July 4, 2020.³⁰ Mechanical ventilation support was required by 28% of participants. Slightly lower 7- and 30-day mortality were reported in patients who received convalescent plasma ≤ 3 days from COVID-19 diagnosis as compared with >3 days from diagnosis, even after adjustment for the effects of some potential confounders. In April 2020, 30-day mortality was 30% for those transfused within 3 days of COVID-19 diagnosis compared to 35% for those transfused ≥ 4 days after diagnosis; mortality declined to 18% and 20% in June 2020 among those 2 groups. Further analysis compared outcomes of a subgroup of 3,082 patients with low, medium, and high SARS-CoV-2 spike sub-unit antibody titers (measured after transfusion). Among those who received a high-titer unit (SARS-CoV-2 IgG signal to cut-off [S/Co] ratio ≥ 18.45), 30-day mortality was 16% compared to 25% in patients who received a low titer unit (SARS-CoV-2 IgG S/Co ≤ 4.62). Limitations of the study include the lack of a non-convalescent plasma comparator arm, potential prognostic differences between individuals transfused earlier and later, changing clinical practice with calendar time, and an increase in high titer units over calendar time. Notably, randomized clinical trials are still needed to determine actual effectiveness and optimal timing of administration.

Benefits and risks: As noted above, benefit is most likely to be achieved with early administration, but as of this writing, there is no robust evidence of benefit from prospective randomized clinical trial data.

The risks associated with the use of convalescent plasma include pathogen transmission, antibody-dependent enhancement of infection,^{22,31,32} allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.^{31,32} 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.³³ An updated analysis of safety among 21,987 patients who received convalescent plasma in the United States as part of the U.S. FDA Expanded Access Program reported low rates of SAEs,³⁴ most of which were judged not to be related to the plasma. Venous thromboembolic disease was reported in <1%, and cardiac events in 3%, transfusion events in

<1%, including 0.18% cases of TRALI and 0.10% cases of TACO. These analyses provide evidence for the safety, not efficacy, 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: Convalescent plasma had been accessible via one of the following mechanisms: a clinical trial, individual eIND, or EAP. The FDA issued an Emergency Use Authorization (EUA) on August 23, 2020. This EUA replaced the FDA prior EAP. This change shifts convalescent plasma from a product for use only under an IRB-approved study protocol and an IND that requires informed consent for participation under a research protocol to a product that can be used clinically without these permissions. Essentially, the EUA moves convalescent plasma from being regulated as a research product to being an investigative agent that can be administered without an IND and IRB approval and oversight, thus reducing the complexity of the use of convalescent plasma.

The FDA EUA specifies the following:

- Plasma donations must be tested for anti-SARS-CoV-2 antibodies, and units with an Ortho VITROS SARS-CoV-2 IgG signal-to-cutoff (S/C) value of <12 must be labeled "COVID-19 Convalescent Plasma of Low Titer." Low titer units may be used if a healthcare provider determines that the benefit of use outweighs the risk.
- Use should be initiated with the administration of one unit (200 mL). Additional convalescent plasma units may be administered based on the patient's clinical response.
- Health care providers must make the FDA Fact Sheet for Patients available to patients prior to use.

NOTE: Under the EAP, convalescent plasma titers for anti-SARS-CoV-2 antibodies were not routinely measured, and blood banks do not necessarily have the processes in place, at present, to measure titers. The FDA has announced a 90-day grace period to allow blood banks and laboratories time to comply with the antibody testing requirements of the EUA. Notice of the grace period was issued on 9/2/2020 and will expire on 12/1/2020.³⁵ The FDA has published a patient information leaflet, and JHMI has issued a consent for the use of convalescent plasma under the EUA (see [Appendix B: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families](#))

Clinical trial participation: This writing group strongly advises that clinicians refer patients to a clinical trial, as early in the course of illness as possible, when treatment with convalescent plasma is most likely to be effective. This is especially the case for patients who are critically ill. As of this writing, there are 2 clinical trials enrolling at Johns Hopkins to study treatment convalescent plasma treatment for patients with a confirmed COVID-19 diagnosis (also see [JH ICTR > Current Approved Therapeutic Protocols for COVID-19](#) for updates as they become available):

- **Hospitalized patients:** [A Feasibility Study Assessing the Safety of Multiple Doses of Anti-SARS-CoV-2 Plasma in Mechanically Ventilated Intubated Patients with Respiratory Failure due to COVID-19.](#)
- **Ambulatory patients:** [Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized, Double-Blind, Controlled, Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma \(HCIP\) vs. Control \(SARS-CoV-2 non-immune\) Plasma Among Outpatients with Symptomatic COVID-19.](#)

Alternative access: The low-quality evidence currently available should be weighed carefully if a clinician and patient decide to pursue treatment with convalescent plasma outside of a clinical trial (i.e., a trial not available or a patient is not eligible for enrollment in an open clinical trial).

- **Critically ill patients:** Clinicians should first send an email to convalescentplasma@jhmi.edu to inquire about the patient's eligibility for the clinical trial noted above.
- **Non-critically ill patients:** If a suitable clinical trial is not available for a patient who is not critically ill, clinicians may contact the blood bank for their institution JHUcovidplasma@jhmi.edu.

For more information and details on COVID-19 Convalescent Plasma, see [FDA Fact Sheet for Health Care Providers: Emergency Use Authorization \(EUA\) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients](#).

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. 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.^{36,37} 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.³⁸ 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.³⁸ 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.

C. Remdesivir

Remdesivir (RDV) is an intravenous antiviral medication that has in vitro activity against SARS-CoV-2 and other coronaviruses.^{39,40} A macaque model treated half of 14 macaques with viral challenge with RDV 12 hours after inoculation.⁴¹ 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).⁴² 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 596 participants with evidence of mild COVID-19 pneumonia (pulmonary infiltrates and SaO₂ ≥94% on room air) who could not be on mechanical ventilation or ECMO.⁴³ 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%). On day 11, when compared with the standard of care group, there was a significant difference in clinical status in the 5-day RDV treatment group.⁴⁴ However, the authors of the study questioned whether there was clinical significance to findings for 5-day RDV treatment compared to standard of care. Moreover, the 5-day RDV group fared better than the 10-day RDV treatment group, and it does not appear that the difference is attributable to a much greater number of adverse events in the 10-day RDV group. This raises concerns about the findings from the comparison of 5-day RDV to the standard of care.

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.⁴⁵

On May 1, 2020, based on the preliminary results from the ACTT-1 and the open-label Gilead GS-US-540-5774 study of 5-day versus 10-day RDV versus standard of care,⁴⁴ the FDA issued an EUA for RDV for the treatment of COVID-19.⁴⁶ 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 Enrollment⁴²	
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 O ₂ or non-invasive ventilation	Favored placebo

7: Invasive mechanical ventilation or ECMO	36
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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^{42,43} 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^{42,43} 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.⁴⁵ 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 [Appendix A: Remdesivir Dosing Guidance Under EUA and Allocation Criteria](#).

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/m² 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.⁴⁷⁻⁵²

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 $\geq 50\%$ in eGFR if RDV is the most likely cause.

Box 2: JHHS Formulary Restriction Status for Remdesivir (RDV)

- Clinicians should evaluate patient eligibility and interest in participating in available RDV clinical trials. Clinical trials are the preferred mechanism for patient access to RDV.
- **Note:** The RDV EUA of [August 28, 2020](#), was broadened to include all hospitalized patients, including those without need for supplemental oxygen; however, this writing group does not recommend RDV for patients who do not require supplemental oxygen. The JHHS Formulary Committee will also evaluate the broadened FDA EUA and issue a decision after October 1, 2020. Therefore, at this time, patients hospitalized within the JHHS must meet the criteria for severe COVID-19 infection to receive RDV. Clinicians may direct appeals for use outside of JHHS indications to the P&T Chair (or designee of) of their institution.
- If a clinical trial is not a viable option for a patient, the clinician can request RDV for a hospitalized patient with confirmed COVID-19 if the patient meets the current JHHS formulary criteria for RDV:
 - COVID-19 positive confirmed during the current episode of care.
 - SaO₂ $\leq 94\%$ on room air or on supplemental oxygen.
 - 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. The use of RDV outside of these restrictions would be non-formulary and must be approved by the institutional P&T chair or designee.

As of this writing, the RDV supply within the JHHS is adequate to meet demand.

D. 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.

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

- 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.⁵³ ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression,⁵⁴ 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.⁵⁵ The best evidence suggests similar or improved outcomes among people on chronic ACE or ARB therapy who develop COVID-19.⁵⁶

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.⁵⁷ A subsequent study reported no increase in viral clearance with HCQ plus azithromycin.⁵⁸ 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.⁵⁹ No clinical efficacy was found in a study of azithromycin against MERS-CoV.⁶⁰

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.⁶¹ 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.⁶¹

DAS 181: 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-2.⁶² 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.⁶³ Reported adverse effects include bronchospasm; dysgeusia; diarrhea; throat irritation; and elevations in alkaline phosphatase, transaminases, creatinine phosphokinase, lactate dehydrogenase, and prothrombin time.

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.⁶⁴

Favipiravir: This inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.^{65,66} 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.⁶⁶ 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.⁶⁵ 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,^{67,68} it has not translated into efficacy in the treatment of any viral infection and this committee recommends against off-label use of hydroxychloroquine for the treatment of COVID-19. Notable studies have reported failure in animal models for Ebola virus and failure in human trials for influenza and HIV.⁶⁹⁻⁷¹ 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.⁵⁷ The lack of pairwise 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 8.⁷² 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.⁵⁸ 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 7.⁷³ 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).⁷⁴

An open-label RCT from China evaluated 62 patients with mild illness who were randomized to receive HCQ or usual care.⁷⁵ 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.⁷⁶ 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.⁷⁷ 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-19.⁷⁸⁻⁸⁰ 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 the 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-19.⁸¹ Multiple RCTs, including those sponsored by the NIH, have been halted because of the futility of HCQ treatment or under-enrollment.⁸²

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.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](#) 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-19.⁸⁴ 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

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 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.⁸⁸ 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.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.

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 intravenous vitamin C in patients with sepsis and acute respiratory distress syndrome.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

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 patients who have 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,^{97,98} the agents recommended for pregnant patients are prednisolone 40 mg by mouth daily or hydrocortisone 80 mg IV 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.⁹⁹ 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 oxygen and a trend toward increased mortality among the sub-group not receiving supplemental oxygen.
- ☑ **IL-6 directed agents:** Tocilizumab is the preferred mAb; however, current data suggest limited or no benefit for general use in hospitalized patients, and robust clinical trial data to support the use of

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

tocilizumab is lacking. Dexamethasone has been found effective and is currently the preferred immunomodulatory agent.

- **Dosing:** If a patient is approved for tocilizumab therapy (preferred*), the clinician should dose it as 8 mg/kg intravenously x 1 dose.¹⁰⁰⁻¹⁰²
 - 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.¹⁰⁰
- 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.¹⁰³ 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 recommendation for the use of dexamethasone is based on findings from the RECOVERY trial⁹⁹ and results from earlier studies of corticosteroid treatment for other types of viral pneumonia. Critical findings from the RECOVERY study are that dexamethasone benefit was greatest among those who were most severely ill (mechanical ventilation) and only after an initial phase of symptoms. The study completed a pre-specified subgroup-compared 28-day mortality analysis by time from symptom onset to initiation of dexamethasone. The investigators reported a reduction in 28-day mortality among patients with >7 days of symptoms but not among patients with \leq 7 days of symptoms. Because this finding is from a subgroup time-to-treatment analysis without adjustment for oxygenation requirement, a symptom duration recommendation is not included in this guidance.

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.^{99,104} 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 28-day primary endpoint for mortality yielded dexamethasone 482/2104 (22.9%) v. placebo 1110/4321 (25.7%) RR 0.83 (0.75-0.93). When subgroups were examined, mortality 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 age adjusted analysis. In patients with ≤ 7 days of symptoms, neither benefit nor harm was associated with dexamethasone treatment.

The findings from the RECOVERY trial may not be generalizable to corticosteroid use overall for the 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 the 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.¹⁰⁵ 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.¹⁰⁶ 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.

Meta-analysis of corticosteroid RCTs: The WHO led a meta-analysis with the primary question of whether corticosteroids reduced 30-day mortality among critically ill patients with COVID-19.¹⁰⁷ The analysis included 7 trials with a total of 1703 patients; 59% of patients were participants in the RECOVERY trial. Six trials were open-label, and one was placebo-controlled. Overall, steroids reduced mortality with an odds ratio of 0.66 (95% confidence interval 0.53 – 0.82). There was also reduced mortality with corticosteroid use by all assessed

subgroups: with or without mechanical ventilation, age \leq or $>$ 60 years, sex, and \leq or $>$ 7 days of symptoms. There was no apparent difference between the use of dexamethasone and hydrocortisone.

Risks and adverse effects: Potential serious adverse effects of short-term corticosteroid use include hyperglycemia, increased risk of infection, fluid retention, and anxiety. Short term corticosteroid use is associated with *Strongyloides* hyperinfection among individuals with risk of infection (e.g., immigrants from endemic countries); testing and treatment should be considered for those at high risk.¹¹³

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

Supply: The supply of tocilizumab and other anti-IL-6 receptor monoclonal antibodies (mAbs) is limited, the availability for ordering is assessed daily, and the benefit is not clear. Therefore, clinical trial participation should be prioritized. Press releases on clinical trials of IL-6 inhibition have stated a lack of effectiveness in primary outcomes (see below). It is possible that specific patients may benefit, including some patients who meet the criteria listed below; therefore, we have kept tocilizumab as a therapeutic option.

Box 5: Criteria for Consideration of COVID-19 Treatment with IL-6R or IL-6 Antibodies		
<ul style="list-style-type: none"> • 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. • If a patient with COVID-19 is suspected of having an evolving cytokine hyperinflammatory syndrome, the clinician may consider 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. 		
<p>1. The patient is \geq18 years old with suspected, evolving COVID-19 hyperinflammatory syndrome.</p> <ul style="list-style-type: none"> • The following factors may increase a patient's risk of poor outcomes (this list may not be comprehensive): <ul style="list-style-type: none"> - Age \geq65 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 	<p>2. AND the patient has progressive hypoxemia* plus one of the following:</p> <ul style="list-style-type: none"> • Sustained respiratory rate $>$30 breaths/min <i>or</i> • Hypotension (decrease in mean arterial pressure [MAP] by 10 mm Hg) <i>or</i> • Fever \geq38.3° C <p>*Sufficiently severe to require at least 4 liters of oxygen to maintain PaO₂$>$92%</p>	<p>3. AND the patient's laboratory values include:</p> <p>An IL-6 level $>$80 pg/mL OR</p> <ul style="list-style-type: none"> • All of the following: <ul style="list-style-type: none"> - D-dimer level $>$1 μg/mL <i>plus</i> - CRP level \geq10 mg/dL <i>plus</i> - Ferritin level $>$750 ng/mL

Box 5: Criteria for Consideration of COVID-19 Treatment with IL-6R or IL-6 Antibodies		
- End-stage kidney disease		
- Advanced liver disease		
<ul style="list-style-type: none"> 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. As of this writing, robust clinical evidence of benefit for patients with COVID-19 is limited. In a recent press release (7/29/20), Roche announced that an RCT that included 450 participants with COVID-19 pneumonia and SpO₂<94% found no significant difference in clinical status or mortality but did report a significantly shorter time to discharge among those who received tocilizumab (20 vs 28 days).^{114,115} It is notable that evidence of hyperinflammation (e.g., elevated CRP), which typically occurs during the period of illness during which tocilizumab is believed to have the greatest chance of benefit, was not one of the inclusion criteria. Roche is continuing with 3 other Phase 2 or Phase 3 tocilizumab RCTs for treatment of COVID-19.

A trial of sarilumab did not reach its primary or secondary endpoints in participants who met enrollment criteria similar to those of the Roche tocilizumab trial.^{116,117} Other data on IL-6 modulators have been provided in case series. 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.¹¹⁸ 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,¹⁰¹ and the concentration-dependent half-life.¹⁰⁰ Additional case series have supported the overall safety of this agent.¹¹⁹

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.¹⁰³ 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.¹²⁰ Long-term use of such mAbs increases the risk of bacterial, mycobacterial, and fungal infections and reactivation of herpes simplex and herpes zoster.¹²⁰ 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.¹²¹⁻¹²³ However, there may be a risk of worsening of bacterial infections with short-term use.¹²⁴ 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:¹²⁰

- 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.¹²⁵ IVIG has been used in the treatment of multiple conditions, including SARS and COVID-19, to control pathogenic inflammation.¹²⁶ A case series of 3 patients reported on the use of IVIG at the point of clinical deterioration and presumed shift to cytokine dysregulation.¹²⁷ 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.¹²⁸ 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.¹²⁹

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.¹³⁰

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.¹³¹ 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 TLR8.¹³² When used in an animal model of influenza, BTK inhibitors rescued mice from lethal lung injury.¹³³ 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.¹³⁴ A case series of 19 patients with COVID-19 treated with acalabrutinib suggested overall safety and a reduction in inflammatory markers.¹³⁵

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Appendix A: Remdesivir Dosing Guidance Under EUA and Allocation Criteria

Johns Hopkins Scarce Resources Group

This is a dynamic document subject to frequent updates

Current version: May 29, 2020

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 <i>requiring mechanical ventilation or ECMO</i>	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 \geq 40 kg <i>NOT requiring mechanical ventilation or ECMO</i>	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 <i>requiring mechanical ventilation or ECMO</i>	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 <i>NOT requiring mechanical ventilation or ECMO</i>	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.

Appendix B: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families

Page 1: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families

Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families

Convalescent plasma is the liquid part of blood that is collected from healthy blood donors who have already recovered from COVID-19 disease. It is currently believed that convalescent plasma contains a part of the donor's immune system that could help you to fight COVID-19 disease. Although the effectiveness of treatment with convalescent plasma is not known, available information shows that the plasma may be helpful, especially for people who are treated early in the course of COVID-19 disease. Treatment with convalescent plasma means you are getting a blood transfusion.

Convalescent plasma is not approved by the United States Food and Drug Administration (FDA). However, on August 23, 2020 the FDA issued an Emergency Use Authorization (EUA) for emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19.

At the current time, COVID-19 convalescent plasma that meets all requirements of the EUA is not routinely available. As a result, on September 2, 2020 the FDA announced a temporary enforcement discretion, which allows us to offer COVID-19 convalescent plasma which meets all of our usual safety standards, but is considered to be investigational by the FDA. This is temporary - eventually plasma that meets the EUA requirements will be available. This type of transfusion is not research, and is not part of an Institutional Review Board (IRB) study.

The purpose of this form is to explain the risks, benefits and alternatives of investigational COVID-19 convalescent plasma.

Risks: Tens of thousands of patients across the United States have already been transfused with investigational COVID-19 convalescent plasma. According to the best information that we have, this plasma is safe and very few people have had a problem with the transfusion. In fact, it is currently believed that investigational convalescent COVID-19 plasma is just as safe as standard plasma.

Risks of Administration Vary, but Include:	Steps Taken to Reduce the Risk May Include:
<p>Transfusion Reaction: (less than 5%)</p> <ul style="list-style-type: none"> Fever, itching and hives are the most common mild symptoms Low blood pressure, difficulty breathing, and organ injury are more serious but also much less common 	<ul style="list-style-type: none"> Before being given, <ul style="list-style-type: none"> except in life-threatening emergencies, donated plasma is matched with your blood type you may be given medicine You will be monitored for any symptoms and the administration will be stopped if necessary
<p>Infection: (less than 0.1%)</p> <ul style="list-style-type: none"> Bacteria Viruses Parasites Prions 	<ul style="list-style-type: none"> Donors are screened prior to being allowed to give blood and all donated blood is carefully tested by suppliers before being sent to the hospital.

Benefits: Although the benefits of COVID-19 convalescent plasma are not known for certain, it is possible that this treatment will help you to recover from COVID-19 disease.

Alternatives: You can choose to continue with other medical therapies, such as pills or medications that are given through your veins. Your doctor or nurse can explain in detail what those treatments are for you. However, at this time, investigational COVID-19 convalescent plasma is the only way for you to be treated with the blood plasma of people who have already recovered from COVID-19.

For Patient/Family

Page 2: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families



CONSENT

**INVESTIGATIONAL COVID-19
CONVALESCENT PLASMA TRANSFUSION
CONSENT OR REFUSAL**

Patient Identification Information

Patient Full Name (Print if not listed above)

I understand that my doctor has recommended that I be transfused with investigational COVID-19 convalescent plasma during my hospitalization for COVID-19.

I understand how and why the investigational COVID-19 convalescent plasma will be administered, as well as the benefits and potential risks. These risks include fever, allergic reactions, transmission of infectious disease, fluid overload, acute lung injury and death. I understand that risks exist despite testing of donor blood and precautions taken during administration.

I have been informed about reasonable medical alternatives to transfusion and their common foreseeable risks and benefits.

Therefore –

CONSENT

I consent to administration of investigational COVID-19 convalescent plasma

REFUSAL

I refuse administration of investigational COVID-19 convalescent plasma.

I understand the risks of my refusal or the limitations placed on my treatment may include serious injury, disability or death. Knowing the risks, I accept full responsibility for this decision.

By signing on page 2, I acknowledge / agree that:

- I have received investigational COVID-19 convalescent plasma administration patient education.
- The indication(s) for administration of investigational COVID-19 convalescent plasma have been explained to me, as well as the benefits, risks and alternatives (if any, with their benefits and risks), and all of my questions have been answered.
- No guarantee has been made concerning the outcome, as the practice of medicine is not an exact science.
- I understand that the convalescent plasma that I am being treated with is considered to be investigational by the FDA.
- My treatment decision is accurately reflected above.

Date

Patient Signature

CONTINUED ON PAGE 2

JHM-000014 (9/20)

Original - Medical Record

Page 3: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families



**INVESTIGATIONAL COVID-19
CONVALESCENT PLASMA TRANSFUSION
CONSENT OR REFUSAL**

Patient Identification Information

*******DECISION-MAKER OTHER THAN PATIENT SECTION*******

Legally Authorized Health Care Decision-Maker:

Date **Print Name** **Signature** (N/A if Telephone Consent)

If the patient would otherwise be consenting on his/her own behalf, but is unable to consent & consent is being obtained from a surrogate decision-maker, refer to Epic Capacity & Advance Care Planning Activity to validate/identify the health care agent (HCA) or primary surrogate decision-maker and confirm documentation of incapacity (n/a for a minor not legally able to consent).

ONLY COMPLETE BELOW IF PERSON GIVING CONSENT IS NOT THE HCA / PRIMARY SURROGATE DECISION-MAKER

The HCA/primary surrogate decision-maker: (check all that apply)

Could not be reached to provide consent

Did not respond to requests for assistance with obtaining consent

Was incapacitated

Was unwilling to make decisions

Other
(describe): _____

*******END DECISION-MAKER OTHER THAN PATIENT SECTION*******

Date Time Signature of Provider Obtaining Consent Title or ID#

Print Provider 1st Name Print Provider Last Name

Date Time Witness Signature (Relationship/Title)

Print Witness Name

Telephone Consent (for telephone consent, witness must be member of the clinical staff)

Interpreter (Complete only if applicable) Remotely via video Remotely via telephone In-person

Date Time Print Interpreter Name Interpreter Signature *(if in person)*