JHMI Clinical Recommendations for Pharmacologic Treatment of COVID-19

Updated December 16, 2020, and replaces the version of November 20, 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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New in the December 16, 2020 Update | Go to current Writing Group recommendations

- This guidance document has been re-organized and now includes a box summarizing the writing group's current clinical recommendations.
- The section on the natural history of COVID-19 disease has been updated.
- JHHS Formulary Management and Medication-Use Policy Committee Restriction for Remdesivir has been added.
- Discussion of randomized clinical trials of convalescent plasma has been updated.
- Information about the FDA EUA for casirivimab/imdevimab has been added, and information about bamlanivimab has been updated.

Contents

I. Purpose

The purpose of this document is to provide clinicians at The Johns Hopkins Hospital (JHH) and the Johns Hopkins Health System (JHHS) with guidance for pharmacologic treatment of inpatient and outpatient 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 using pharmacologic agents for the treatment of patients diagnosed with COVID-19.

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](#).

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

Available non–JHH-specific guidelines: See 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 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](#)

II. Natural History of COVID-19 Disease

The natural history of COVID-19 varies considerably among those infected with SARS-CoV-2, most likely due to multiple factors, including, but likely not limited to a patient's health and comorbidities when infected, the exposure inoculum, and potentially, viral genetics. Between 8% and 50% of individuals infected with SARS-CoV-2 have asymptomatic or subclinical infection.[1] Onset of symptomatic infection typically occurs within 4 to 5 days (median) of exposure. It appears that the peak level of viremia is reached at about the time of symptom onset, with high viremia lasting from 2 days prior until approximately 5 days after symptom onset with no detectable viable virus 8 to 10 days after symptom onset in normal hosts[2-6] Infectivity parallels high viral carriage, with the period of contagiousness starting 2 to 5 days prior to symptom onset and extending to approximately 5 days after symptom onset.

Symptomatic infection: Symptoms typically start with headache, myalgia, and upper respiratory symptoms, including sore throat; these initial symptoms may be followed a few days later by fever, cough, diarrhea, and anosmia. Overall, any one of these symptoms is observed in between 20 and 80% of patients. The majority of symptomatic patients appear to have mild disease and do not require hospitalization. Patients with mild disease often recover after 7 days of symptoms.

Severe disease: More severe disease leading to hospitalization occurs at a mean of 7 days after symptom onset.[7,8] A marker of more severe disease is the onset of COVID-19 pneumonia, characterized by fever, cough, fatigue, myalgia, dyspnea, and dyspnea on exertion. Radiographic findings typically include ground-glass opacities in the lungs; lymphocytopenia is also commonly observed.[9,10] Imaging is characterized by diffuse,

bilateral, ground-glass opacities. Patients with severe disease may become severely hypoxic and require high-flow oxygen support or mechanical ventilation to maintain oxygen saturation levels >92%.

Progression to severe COVID-19 and the need for hospitalization are associated with multiple risk factors, including advanced age, obesity, hypertension, diabetes, chronic lung disease, tobacco use, immune deficiencies, cancer, limited access to health care, and possibly residence in a long-term care facility.[11-16]

Hyperinflammatory syndrome: Some patients progress to disease characterized by hyperinflammation that can include acute respiratory distress syndrome (ARDS) and may occur approximately 5 to 10 days after symptom onset. Fevers characterize the COVID-19 hyperinflammatory syndrome along with rapid worsening of respiratory status; alveolar filling pattern on imaging; often marked elevations in laboratory markers associated with specific inflammatory pathways, such as interleukin-6 (IL-6);[17,18] and nonspecific markers of inflammation, including D-dimer, C-reactive protein (CRP), and ferritin. Patients typically have increased levels of cytokines, including IL-6, IL-2R, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-alpha (TNF-α), all of which decline as patients recover.[19] Lymphopenia has also been reported, with declines in CD4+ T cells and CD8+ T cells.[19] 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).[20-26] Patients may progress to multiorgan failure as a result of the cytokine-mediated hyperinflammation.[27]

Vascular disease: Microvascular thrombosis and venous thromboembolism also occur with severe COVID-19.[28-30]

Goals and optimal timing of treatment: 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 an excessive inflammatory response, or a nonspecific adjuvant impact on the host, as illustrated in the figure below.

- **Outpatient treatment:** The primary goal of outpatient treatment is to limit disease progression. This requires treatment initiation early in the disease course, either prior to symptom onset or shortly thereafter. The only medications currently approved for outpatient treatment are bamlanivimab and casirivimab/imdevimab, monoclonal antibodies that target the SARS-CoV-2 spike protein.

- **Inpatient treatment:** The 2 goals for inpatient treatment are limiting disease progression through antiviral activity and limiting COVID-19-related inflammation. The 2 available antiviral agents are remdesivir and convalescent plasma.

Figure. Schematic of Clinical Course of Severe COVID-19

Representation of SARS-CoV-2 RNA levels, common symptoms, and possible timing of therapeutics with greatest benefit.

III. Current Writing Group Recommendations for JHMI

Current Writing Group recommendations for pharmacologic treatment discussed in this document are summarized in Box 2, below. Links are provided to the sections of the document in which additional information and supporting evidence is provided.

Box 2: Summary of Clinical Recommendations for Pharmacologic Treatment of COVID-19

- **Clinical trial participation:** Participation in available clinical trials is strongly recommended for patients who meet inclusion criteria.

- **Infectious diseases consultation:** Prescribing clinicians should consult with infectious diseases clinicians to treat any solid organ or bone marrow transplant recipient.

- **Remdesivir:** This writing group recommends that clinicians prescribe RDV for the treatment of hospitalized patients with COVID-19 who meet the JHHS formulary criteria (more information).

- **COVID-19 convalescent plasma:** There is an FDA EUA to treat hospitalized patients with COVID-19. This writing group recommends that if clinicians decide to administer convalescent plasma, they should do so as soon after infection as possible (i.e., ≤7days after symptom onset) when this treatment is likely to be most effective (more information).

- **Bamlanivimab and casirivimab/imdevimab:** These medications are available for outpatient treatment only of COVID-19 patients with risk factors for severe COVID-19. Both regimens are being provided by referral at the Baltimore Convention Center Field Hospital or 3 other locations in the state of Maryland (more information).

- **Corticosteroids:** Dexamethasone is recommended for treatment of COVID-19 patients who have either a persistent need for non-invasive supplemental oxygen to maintain SaO2 ≥94% or who require mechanical ventilation (more information).

  - The Division of Hematology has developed recommendations for VTE prophylaxis.

- **Targeted immune modulators:** The use of tocilizumab and baricitinib for the treatment of COVID-19 is recommended only for patients who are enrolled in a clinical trial. More information.

- **Agents to avoid for treatment of COVID-19:** Because there is no or inadequate evidence of efficacy or effectiveness, the following agents are not recommended for treatment of COVID-19 specifically in hospitalized patients (but they may be administered in clinical trials). There is no evidence that any of these agents are harmful when prescribed for the treatment of other conditions in patients with COVID-19: ACE inhibitors, ARBs, azithromycin, baloxavir marboxil, darunavir/ritonavir, famotidine, favipiravir [a], fluvoxamine, hydroxychloroquine, NSAIDs, ivermectin, lopinavir/ritonavir, nitazoxanide, oseltamivir, ribavirin, umifenovir [not FDA-approved or available in the United States], vitamin C, vitamin D, zinc (more information).

Abbreviation key: ACE, angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; EUA, Emergency Use Authorization; FDA, U.S. Food and Drug Administration; HCQ, hydroxychloroquine; JHHS, Johns Hopkins Health System; IVIG, intravenous immune globulin; NSAID, nonsteroidal anti-inflammatory drug; P&T, Johns Hopkins Medicine Pharmacy and Therapeutics Committee; RDV, remdesivir; SaO2, oxygen saturation; ULN, upper limit of normal

IV. Approaches to Pharmacologic Treatment of COVID-19

A. Viral Suppression

Approaches for suppression of SARS-CoV-2 infection include direct antiviral activity through inhibition of viral replication (antiviral molecules), viral neutralization through introducing exogenous antibodies (neutralizing monoclonal antibodies and convalescent plasma), and upregulating the immune response (interferon).

☐ Remdesivir

Remdesivir (RDV) is an intravenous antiviral medication that has *in vitro* activity against SARS-CoV-2 and other coronaviruses.[31,32]

The ACTT-1 clinical trial (double-blind, placebo-controlled; sites in North America, Europe, and Asia) randomized 1,062 participants with severe COVID-19 pneumonia, defined as infiltrates on imaging or SaO2 <94%, to receive either 10 days of RDV or placebo. RDV was stopped for patients who were ready for discharge before completing 10 days of treatment. Through 28 days of observation following randomization, patients in the RDV arm had a median time to recovery of 10 days compared to 15 days among placebo arm patients (p<0.001).[33] Results suggested a trend, though not significant, toward reduced mortality among those receiving RDV, with Kaplan-Meier 29-day estimates of 11.4% for the RDV arm and 15.2% for the placebo arm. Subgroup analysis found that patients who required supplemental oxygen but not mechanical ventilation or extracorporeal membrane oxygenation (ECMO) had the greatest reduction in time to recovery. There was no difference in outcomes among those who were mechanically ventilated or on ECMO. In addition, there was a significant 60% reduction in 29-day mortality among individuals who required supplemental oxygen but not ventilation or ECMO and received RDV.

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.[34] 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.[35] 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.

The Solidarity study is a pragmatic open-label RCT of remdesivir, hydroxychloroquine, lopinavir/ritonavir, and sub-cutaneous interferon-beta 1a.[36] The study was conducted in 405 hospitals in 30 countries and depended on using medications routinely available in each hospital. A total of 11,266 hospitalized adults were included, with 2750 randomized to 10 days of remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir/ritonavir, 651 to lopinavir/ritonavir plus interferon, 1412 to interferon alone, and 4088 to no study drug. Only 2-6% of participants were reported to cross-over from the allocated arm to another arm. Day 28 mortality was 12%. There was no reduction in death among those who received remdesivir compared to standard of care (risk ratio 0.95, p=0.5). There was also no difference in terms of the need for mechanical ventilation or time to discharge. This study did not include clinical improvement assessments, in comparison to the ACTT-1 study. Fewer data

points were collected in the Solidarity trial. It is unclear why no benefit was seen in this study in contrast to the reduced time to recovery and signal for decreased mortality seen in the ACTT-1 study.

Analysis of the experience at JHMI suggests improved outcomes among patients who received RDV compared to similar patients who did not.[37]

On October 22, 2020, the FDA approved remdesivir for the treatment of adult and pediatric patients ≥12 years requiring hospitalization for COVID-19 (see FDA > Highlights of Prescribing Information for RDV).

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 a shorter duration of symptoms (<10 days). 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 7 to 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). Based on oxygen requirement at enrollment, subgroup analysis 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[33]	
Illness Score at Enrollment (ACTT-1 category assignment)	**Number Needed to Treat to Prevent 1 Death**
4: No supplemental oxygen needed	No difference (hazard ratio: 0.82)
5: Supplemental oxygen via nasal cannula	12 (hazard ratio: 0.3)
6: High flow O2 or non-invasive ventilation	No difference (hazard ratio 1.0)
7: Invasive mechanical ventilation or ECMO	No difference (hazard ratio 1.1)

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

Side effects and adverse events: 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).

Adverse events (from RDV or COVID-19) reported in clinical trials[34,38] 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[34,38] 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.[39] 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.

Discharge before completion of treatment course: RDV administration should not delay hospital discharge. If a patient has received less than a complete course of RDV and meets discharge criteria, RDV should be discontinued.

Dosing: See FDA > Highlights of Prescribing Information for RDV.

Drug-drug interactions: RDV is a substrate for CYP2C8, CYP2D6, CYP3A4, and OATP1B1 and an inhibitor of CYP2A4, OATP1B1, and OATP1B3. The antagonism 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. Note that drug-drug interactions have not been fully assessed with RDV. Patients who are taking multiple medications with CYP metabolic pathways may be at increased risk for adverse drug-drug interactions. There are currently no firm recommendations for dose adjustment; however, concomitant use with strong cyp3A4 inducers such as rifampin may reduce RDV levels.[40] In situations of uncertainty, clinicians are advised to review potential drug-drug interactions with a clinical pharmacologist.

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 > Highlights of Prescribing Information for RDV). Clinical trials of COVID-19 treatment have excluded patients with an eGFR <30 mL/min/m^2 or 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 using RDV in patients with eGFR <30 mL/min/m2 unless the potential benefit outweighs the potential risk (see FDA fact sheet).

At JHMI, no decline in kidney function was found in recipients of solid organ transplants with serum creatinine levels between 1.0 and 2.5 mg/dL when treated with RDV.* A case series of 46 patients with ESRD on dialysis or a range of CKD stages who received RDV did not identify any increased risk of side effects or further renal impairment.[41] In addition, IV voriconazole, another medication that also contains SBECD, has been extensively used and evaluated in patients with varying degrees of severe kidney disease and kidney impairment without evidence of harm.[42-48]

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 >10 times the 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:** Clinicians should discontinue RDV if there is a decline ≥50% in eGFR while evaluating for causes of acute kidney injury.

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*Author personal communication with Robin Avery, MD; November 5, 2020

Box 3: JHHS Formulary Management and Medication-Use Policy Committee Restriction for Remdesivir (12/3/2020)

· Also see Appendix B: JHH Pharmacy and Therapeutics Committee Memo: Remdesivir Formulary Restriction and Order Review Process (December 11, 2020; effective December 15, 2020).

Formulary restriction: Patients must meet all of the following criteria to initiate remdesivir. All courses are restricted to 5 days of therapy.

- RNA or antigen test indicating active COVID-19 infection (not serology)

- ≤10 days since COVID-19 symptom onset

- Presence of respiratory compromise at the time of clinical evaluation defined by one or more of the following:

  – Sa02 ≤ 94% on room air for ≥1 hour

  – Requiring supplemental oxygen to maintain Sa02 >94% for ≥1 hour

  – Documented sustained RR ≥24 breaths per minute

- Not receiving mechanical ventilation or ECMO, unless these modalities were initiated for the first time within the past 24 hours

- ALT ≤10 times the ULN

Formulary Comments:

- The above criteria apply to all patients, including those with immune compromise, malignancy, or solid organ transplant history.

- Renal dysfunction is not a contraindication to remdesivir therapy. The package labeling does not recommend use in patients with renal impairment. If a patient has an eGFR <30 mL/min there must be documentation in the record that the prescriber has discussed with the patient both the FDA package insert recommendation and their assessment that the benefits of remdesivir therapy outweigh the potential harms, and the patient has agreed to continue with remdesivir therapy.

- If ALT increases to >10 times the ULN or the patient develops other signs or symptoms of hepatotoxicity, remdesivir must be discontinued.

- Remdesivir is a substrate of CYP3A4. At this time, no drug-drug interaction studies have been performed. Use caution when giving remdesivir with CYP3A4 inhibitors (e.g., azole antifungals) or inducers (e.g., rifampin).

- Patients transferred to JHHS from an outside hospital on remdesivir can complete their 5-day course of therapy (without formulary review).

- Patients well enough for discharge home can be discharged without completing their current course of remdesivir.

☐ Convalescent Plasma

Rationale: The 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.[49-53] 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.[53] To be most effective, convalescent plasma should be administered as soon after infection as possible.

RCTs of convalescent plasma:

- An open-label RCT from China conducted from mid-February through April 1, 2020, included 103 participants with a median duration of 30 days of symptoms who were randomized 1:1 to receive convalescent plasma or standard treatment. At the time of randomization, 94% of participants in the convalescent plasma arm had experienced >14 days of symptoms.[54] The primary outcome, clinical improvement within 28 days, was similar in the 2 arms.

- An RCT 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.[55] At the time of enrollment, participants had experienced a median of 10 days of symptoms. Most had high levels of neutralizing antibodies, which may explain the reported similar overall outcomes between treatment and control groups.

- A placebo-controlled RCT from Argentina randomized 333 patients with severe COVID-19 2:1 to convalescent plasma or placebo at a median of 8 days from the time of symptom onset.[56] Day 30 outcomes were similar between trial arms; overall mortality was 11% in the convalescent plasma arm and placebo arms.

- A different placebo-controlled RCT from Argentina randomized 160 ambulatory patients with <48 hours of COVID-19 signs and symptoms 1:1 to convalescent plasma and placebo.[57] The participants met the additional inclusion criteria of age ≥75 years or 65 to 74 years with comorbidities. Treatment was initiated <72 hours from symptom onset. At day 15, more participants in the placebo arm (31%) compared to the convalescent plasma arm (16%) developed severe respiratory disease (p=0.02); 2 convalescent plasma and 4 placebo arm participants died.

The results of these RCTs suggest that early use of convalescent plasma (<72 hours after symptom onset) may reduce the progression of respiratory disease, and later use (e.g., >7 days after symptom onset) does not improve clinical outcomes.

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 (≤3 days); plasma with higher antibody titers also improved outcomes. 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.[58] 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. 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). The study's limitations 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.

Benefits and risks: As noted above, the benefit is most likely to be achieved with early administration, within 7 days (or possibly 3 days as in the study was a statistically significant benefit) of symptom onset and possibly prior to hospitalization.

The risks associated with the use of convalescent plasma include pathogen transmission, antibody-dependent enhancement of infection,[53,59,60] allergic transfusion reactions, transfusion-associated circulatory overload

(TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.[59,60] 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 at 4 hours post-administration occurred in <1% of patients.[61] An updated analysis of safety among 21,987 patients who received convalescent plasma in the United States as part of the U.S. FDA EAP reported low rates of SAEs,[62] 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 required antibody labeling is not specifically for neutralizing antibodies. 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 prior FDA EAP. This change shifts convalescent plasma from a product for use only under an IRB-approved study protocol and an investigational new drug protocol (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 or with the Mount Sinai COVID-19 ELISA IgG Antibody Test 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. See the FDA December 1, 2020, COVID-19 Update for more information.

- 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.

- Healthcare 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. The FDA has provided an initial 90-day grace period to allow blood banks and laboratories time to comply with the antibody testing requirements of the EUA. To comply with the EUA, as of 12/1/2020, the antibody titer of all convalescent plasma units must be determined prior to use.[63]

The FDA has published a patient information leaflet, and JHMI has issued consent for the use of convalescent plasma under the EUA (see Appendix A: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families).

For more information: 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.

Box 4: Convalescent Plasma Access

- **Clinical trials:** This writing group strongly advises that clinicians refer patients to a clinical trial, as early in the course of the 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, 2 clinical trials (one outpatient and one in critically ill patients) are enrolling at Johns Hopkins to study 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; a third trial of convalescent plasma is not for treatment but prevention of infection following close exposure.

  - 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 for patients outside of a trial:** The low-quality evidence currently available should be weighed carefully if a clinician and patient decide to pursue treatment with convalescent plasma for hospitalized patients (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.

- **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. Antibody Mediation or Neutralization

Theoretically, monoclonal antibodies and convalescent plasma will neutralize SARS-CoV-2 before a patient develops high titers of neutralizing antibodies.

☐ Monoclonal and Polyclonal Neutralizing Antibodies

Although their mechanism of action is much the same as that hypothesized for convalescent plasma, monoclonal (mAbs) or polyclonal antibodies (pAbs) are synthetic. Those currently furthest along in development, bamlanivimab and REGN-COV2, are directed at the SARS-CoV-2 spike protein.

Casirivimab/imdevimab: Preliminary analysis included 275 outpatients with COVID-19 confirmed by nucleic acid testing who were enrolled and randomized 1:1:1 to receive a low or high dose of REGN-COV2 or placebo.[64] Prior to receiving the Ab, 45% of patients were seropositive, and 41% were seronegative; serostatus was not determined for 14% of participants. REGN-COV2 reduced SARS-CoV2 PCR levels in samples from the nasopharynx through day 7. The reduction was most notable for participants who were seronegative on enrollment and had the highest viral loads. A 95% reduction in viral load was found in this group when compared to the placebo group. Symptom resolution occurred in 13 days in the placebo group, in 8 days in the high-dose group (p=0.22), and in 6 days in the low-dose group (p=0.09). These findings led the FDA to issue an EUA on November 21, 2020.

An RCT of REGN-COV2 for hospitalized patients with varying illness severity found that treatment may be more harmful than beneficial. As a result, enrollment in this trial has been put on hold.

Bamlanivimab (LY-CoV555): A phase II clinical trial randomized 452 outpatients to receive a low, medium, or high dose of the mAb or placebo, with a change in SARS-CoV-2 RNA at day 11 compared to baseline as the primary endpoint.[65] Participants had confirmed COVID-19 and at least 1 COVID-19-related symptom but no need for supplemental oxygen. When compared with placebo, a significant difference was found only in the medium-dose bamlanivimab arm. The day-3 RNA was a half log lower in the pooled mAb arms than the placebo (a decline of 1.35 log compared to the 0.85 log). More clinically relevant was a reduction in emergency department visits and (predominantly) hospitalization in the pooled mAb arms (1.6%) compared to the placebo arm (6.3%), with the greatest difference reported in subgroup analysis with participants aged ≥65 years or with a BMI ≥35kg/m^2 (4% compared to 15%). Of note, the median time from onset of presentation to time of administration was 4 days. Any potential benefit of the monoclonal is likely derived with early administration. Adverse effects were similar in the 2 groups, and there were no serious adverse events in either group. The FDA issued an [Emergency Use Authorization (EUA) for bamlanivimab on November 10, 2020](). The criteria and logistics for the use of this medication are described below.

Guidance for the use of bamlanivimab and casirivimab/imdevimab: These medications are not FDA-approved for treatment of COVID-19; they can be accessed only through clinical trials and the FDA EUAs for outpatients (see hyperlinks above). This writing group recognizes existing data are insufficient to support a recommendation and encourages clinical trial participation for patients who meet eligibility criteria. To maximize any potential benefit, clinicians who decide to treat individual patients with either of these regimens should aim for use early after infection or disease onset (<7 days).

Outpatient treatment only: Early clinical trial data suggest that patients who have severe COVID-19 (i.e., hospitalization is required) may be harmed by treatment with either of these regimens. Clinicians *may consider* using this medication for *outpatient* treatment of patients with mild symptomatic COVID-19 disease who do not require supplementation oxygen, have experienced 2 to 10 days of symptoms, and are at high risk for severe COVID-19, the criteria for which are described in the EUA. The EUA specifies that a patient must meet 1 of the following criteria:[66]

- BMI ≥35 kg/m^2
- Chronic kidney disease (eGFR <60 mL/min/mm^3)
- Diabetes
- Immunosuppressive disease with ongoing immune deficiency
- Currently receiving immunosuppressive treatment
- ≥65 years old
- ≥55 years old *AND* cardiovascular disease OR hypertension OR chronic respiratory disease
- Are 12 to 17 years of old AND have at least one of the following comorbidities:
  - BMI ≥85th percentile for their age and gender (based on growth charts from the Centers for Disease Control and Prevention [CDC] growth charts)
  - Sickle cell disease
  - Congenital or acquired heart disease
  - Neurodevelopmental disorder (e.g., cerebral palsy)
  - Medical-related technology-dependent (e.g., tracheostomy)
  - Asthma or other chronic respiratory diseases that requires daily medication

Dosing and administration: Bamlanivimab is administered as a one-time intravenous infusion (over at least 60 minutes) of 700 mg. The administration must take place in a staffed setting equipped to respond to and treat severe infusion reactions (e.g., anaphylaxis) and monitor patients for 1 hour after completion of the infusion.

Casirivimab 1200 mg/imdevimab 1200 mg is administered as a one-time intravenous infusion (over at least 60 minutes) of each of the 2 regimen components. The administration must take place in a staffed setting equipped to respond to and treat severe infusion reaction (e.g., anaphylaxis) and monitor patients for 1 hour after completion of the infusion.

Current availability: Bamlanivimab and casirivimab/imdevimab are being administrated at the following 4 Maryland locations: Baltimore Convention Center Field Hospital, Takoma Park (facility to be determined), Title Health Peninsula, and Western Maryland Medical Center. If both agents are available, they will be administered on alternating days.

For more information: See Bamlanivimab Fact Sheet for Health Care Providers, Fact Sheet for Patients, Parents and Caregivers Emergency Use Authorization (EUA) of Bamlanivimab for Coronavirus Disease 2019 (COVID-19), Casirivimab/Imdevimab EUA Letter of Authorization, and Frequently Asked Questions on the Emergency Use Authorization for Casirivimab and Imdevimab.

☐ 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.[67,68] 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.[69] Patients with <7 days of symptoms who received IFN beta-1b had a shorter time to negative reverse transcription PCR results for SARS-CoV-2 and to symptom resolution.[69] 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. Immune Modulation

Box 5: 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,[70,71] 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.[72] 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.

Box 5: Recommendations for the Use of Immune Modulatory Agents to Treat COVID-19

☑ **Other immune modulators:** Use of the following agents as treatment for COVID-19 is recommended only in the setting of a clinical trial, partly because of uncertainties about combined immune suppression when used with dexamethasone (see Section E for details on the potential mechanism of action):

– Anti–GM-CSF mAb

– Anti-IL1

– Convalescent plasma or serum-containing neutralizing antibodies

– Cyclosporine A

– Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)

– IL-6 directed agents

– Intravenous immune globulin (IVIG)

– Janus kinase (JAK) inhibitors

– TNF-α inhibitors

☐ Corticosteroids

The recommendation for the use of dexamethasone is based on findings from the RECOVERY trial[72] and results from earlier studies of corticosteroid treatment for other types of viral pneumonia. The RECOVERY study's critical findings 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 ≤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.[72] The 2,104 patients 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 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 the age-adjusted analysis. In patients with ≤7 days of symptoms, neither benefit nor harm was associated with dexamethasone treatment.

The RECOVERY trial findings may not be generalizable to corticosteroid use overall for the treatment of COVID-19. Dexamethasone has minimal mineralocorticoid activity, leading to less 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, this study's mortality rate was higher than what has been reported in the U.S.[73] In addition, the use of 28 day-mortality endpoints may obscure later complications 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. [74] 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/intensive care unit 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.[75] 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 ≤ or > 60 years, sex, and ≤ 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.[76]

☐ Targeted Immune Modulators

Recommendation: This writing group recommends the use of this class of agents for COVID-19 therapy only for patients who are enrolled in a clinical trial. RCT results reported to date have found no or limited difference in outcomes when treatment with targeted immune modulators is compared with placebo or standard of care.

RCTs results have been reported to date for several immune modulators, including for those directed toward the IL-6 and IL-6 receptors (tocilizumab, sarilumab), the Janus Kinase pathway (JAK; baricitinib), and IL-1 pathway (anakinra). Clinical trials of other agents, including Bruton tyrosine kinase inhibitors (BTK; acalabrutinib), are underway. These agents have the theoretical appeal of reducing what appears to be a COVID-19-associated hyperinflammation syndrome. Case series and cohort studies suggested that specific immune modulatory agents improved COVID-19 outcomes among patients with severe disease.[25,77-81] Only baricitinib, a JAK inhibitor, has RCT evidence of improving outcomes (length of stay) for COVID.

IL-6: The most favorable results for IL-6 inhibitors come from case series and cohort studies.[78,79 80 79 82,83] RCTs of tocilizumab and sarilumab have failed to identify significant benefit. A placebo-controlled RCT study of 242

patients with fever, pneumonia, and laboratory evidence of inflammation randomized to tocilizumab or placebo found no difference in clinical worsening or death at day 14 and day 28 endpoints.[84] Two open-label RCTs of patients with COVID-19 pneumonia or pneumonia and fever and elevated CRP reported no difference in survival at 28 days[85] or clinical progression at 14 days[86]; the later trial was halted early due to perceived futility. In a 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).[87,88] The Roche EMPACTA study of tocilizumab reported a reduction in mechanical ventilation in patients with COVID-19 pneumonia in a double-blind RCT of 389 patients.[89] The hazard ratio of progression to mechanical ventilation was 0.56 (p=0.03) among participants randomized to the tocilizumab arm compared to the placebo arm. However, the time to improvement was not significantly different between arms, and mortality was similar (10.4% in the tocilizumab arm and 8.6% in the placebo arm). The incidence of infections was similar in both arms. A trial of sarilumab did not reach a difference between arms in its primary or secondary endpoints.[90,91]

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.[92] Hence, these inhibitors may be useful against uncontrolled inflammation, such as that seen with COVID-19. The ACTT-2 study, which compared baricitinib and remdesivir to placebo and remdesivir, reported a statistically significant difference in the primary outcome of time to recovery. Participants in the baricitinib arm reached hospital discharge one day earlier than placebo patients.[93] The effect of combined immune suppression from both dexamethasone, a recommended COVID-19 therapeutic agent, and baricitinib is unclear. As a result, baricitinib is not recommended for use with COVID-19 outside of clinical trials despite an FDA EUA for use 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,[21] 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.[94] No RCTs have been reported for anakinra.

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.[95]

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

BTK inhibitors: BTK inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, are FDA-approved for treating 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.[97] When used in an animal model of influenza, BTK inhibitors rescued mice from lethal lung injury.[98] A case series report on patients who developed COVID-19 while receiving ibrutinib for Waldenstrom macroglobulinemia suggested no worsening in the outcome and possibly less of an inflammatory response.[99] A case series of 19 patients with COVID-19 treated with acalabrutinib suggested overall safety and a reduction in inflammatory markers.[100]

GM-CSF inhibitors: Lenzilumab neutralizes human GM-CSF. In vitro data suggest it may limit CRS. Given the role of GM-CSF in inflammation and COVID-19,[101] lenzilumab may be useful in the management of COVID-19. RCTs are in progress.

☐ 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.[102] IVIG has been used to treat multiple conditions, including SARS and COVID-19, to control pathogenic inflammation. [103] A case series of 3 patients reported using IVIG at the point of clinical deterioration and presumed shift to cytokine dysregulation.[104] 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.

V. Agents With Speculative Effect to Avoid as COVID-19 Treatment

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Box 6: Recommendations for Agents to Avoid as Treatment for COVID-19 Specifically

☑ Because there is no or inadequate evidence of their efficacy or effectiveness or evidence of a lack of efficacy, the following agents are not recommended for treatment of COVID-19, specifically, in hospitalized patients, except when administered in a clinical trial. There is no evidence that any of the following agents are harmful when prescribed for the treatment of other conditions in patients with COVID-19.

  · 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)
  · Fluvoxamine
  · 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
  · Vitamin D
  · 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.

There is no plausible evidence of in vitro activity for the agents listed above, 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.[105] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression,[106] 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.[107] The best evidence suggests similar or improved outcomes among people on chronic ACE or ARB therapy who develop COVID-19.[108]

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 discontinuing 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.[109] A subsequent study reported no increase in viral clearance with HCQ plus azithromycin.[110] 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.[111] No clinical efficacy was found in a study of azithromycin against MERS-CoV.[112]

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.[113] 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.[113]

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.[114] 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.[115] 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.[116]

Favipiravir: This inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.[117,118] An open-label, non-randomized clinical trial comparing favipiravir with LPV/RTV suggested that favipiravir reduced the duration of viral shedding and led to a more rapid improvement in chest computed tomography findings.[118] 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.[117] This drug is not approved by the FDA and is not available in the United States.

Fluvoxamine: It has been hypothesized that this selective serotonin reuptake inhibitor may modulate the immune response through the sigma-1 receptor agonism. A placebo-controlled *outpatient* RCT randomized 152 adults with confirmed SARS-CoV-2 infection to receive 15 days of escalating doses of fluvoxamine (n=80) or

placebo (n=72). The primary endpoint was clinical deterioration. Clinical deterioration occurred in 0 of the participants in the fluvoxamine arm and in 6 (8.3%) of those who received a placebo. Pneumonia and gastrointestinal adverse events occurred more often in the placebo arm than the active arm. More data are required to understand the potential use of this agent in patients with COVID-19.

Hydroxychloroquine (HCQ): Although HCQ has in vitro activity against SARS-CoV-2 and some other viruses,[119,120] 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.[121-123] 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.[109] 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.[124] 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.[110] 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.[125] 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).[126]

An open-label RCT from China evaluated 62 patients with mild illness who were randomized to receive HCQ or usual care.[127] 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 ARDS within 7 days.[128] 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.[129] 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.[130-132] 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 to use 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.[133] Multiple RCTs, including those sponsored by the NIH, have been halted because of the futility of HCQ treatment or under-enrollment.[134]

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.[135] 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.[136] Similar to ACE inhibitors and ARBs, ibuprofen has been reported to upregulate ACE2 receptors. However, no published clinical data currently suggest an increased risk in patients with COVID-19 using NSAIDs. In general, acetaminophen is preferred for the treatment of fever in patients with COVID-19, but therapy should be individualized for hospitalized patients, considering kidney and liver function.

Ivermectin: There is in vitro evidence that ivermectin inhibits SARS-CoV-2 replication.[137] Several retrospective cohort studies have compared outcomes among patients who received ivermectin to those who did not, with mixed results regarding ivermectin's effect on outcomes.[138-142] There are substantial limitations to both positive and negative studies. A small RCT of 72 participants in 3 arms reported no difference in primary outcomes between study arms but did report more rapid clearance of viral RNA in the ivermectin arms.[143]

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).[144] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[145] 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.[146] 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.[147] The large UK RECOVERY trial reported no reduction in 28-day mortality, duration of hospital stay, or disease progression among 1,616 patients randomized to receive LPV/RTV compared to 3,424 patients who received usual care.[148]

Nitazoxanide: This agent has been tested in vitro against MERS-CoV and SARS-CoV-2 and found to have activity.[149] 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.[150]

Umifenovir: This agent was routinely used in China to treat patients with COVID-19.[151] 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.[152] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[153]

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 ARDS.[154] 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.

Vitamin D: Patients with low vitamin D levels appear to be at increased risk for several infections, and vitamin D has been proposed to play a role in ARDS.[155] It has been suggested that vitamin D supplementation may reduce the severity of COVID-19. In an open-label RCT of vitamin D supplementation among patients with COVID-19 pneumonia, 76 patients were randomized 2:1 to receive vitamin D or standard care alone.[156] Vitamin D was dosed as 0.532 mg calcifediol (a D3 analog) on day 1, 0.266 mg on days 3 and 7, and then weekly until discharge. Intensive care was required for 50% (n = 13) of the standard care group compared to 2% (n = 1) of the vitamin D group (p<0.001). This pilot study results suggest a possible role for vitamin D supplementation, which must be confirmed through additional, larger RCTs.

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.[157]

VI. Development of This Guidance

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.

Box 7: COVID-19 Pharmacologic 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

- **Contributing members:**

  – 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

  – Kate Dzintars, PharmD, Clinical Pharmacy Specialist, Division of Infectious Disease

  – Brian T. Garibaldi, MD, Director, Johns Hopkins Biocontainment Unit; Associate Professor of Medicine

  – Elisa Ignatius, MD, MSc, Fourth Year Fellow, Infectious Diseases, Clinical Pharmacology

  – Tania Jain, MBBS, Assistant Professor of Oncology

  – Andrew Karaba, MD, PhD, Fourth 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

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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.

Guiding principles:

- 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. The body of available clinical data is growing rapidly, and RCTs with strong study design and adequate sample size are considered the best possible source of data on which to base specific recommendations.

- 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.

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.

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Appendix A: 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.

<u>Risks</u>: 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:

Transfusion Reaction: (less than 5%)
• 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
	• Before being given,
	   o except in life-threatening emergencies, donated plasma is matched with your blood type
	   o you may be given medicine
	• You will be monitored for any symptoms and the administration will be stopped if necessary

Infection: (less than 0.1%) • Bacteria • Viruses • Parasites • Prions	• 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.

<u>Benefits</u>: 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.

<u>Alternatives</u>: 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.
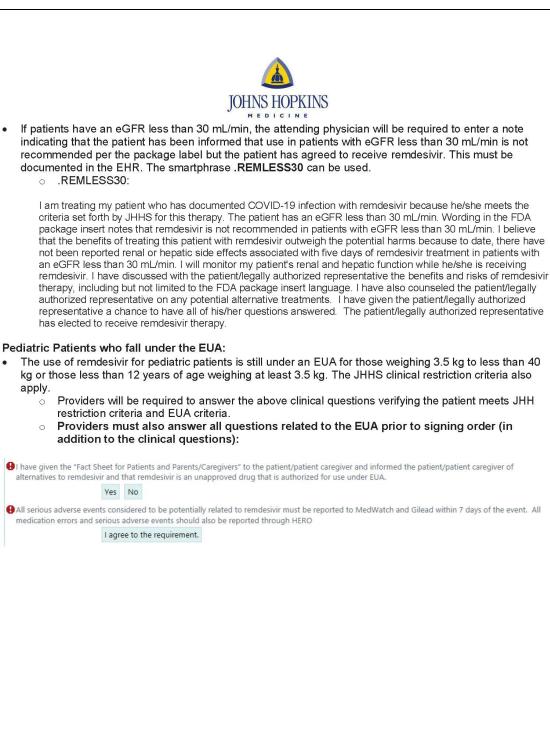
For Patient/Family

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

JOHNS HOPKINS
M E D I C I N E

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

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

JOHNS HOPKINS
M E D I C I N E

**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)*

JHM-000014 (9/20)   Original - Medical Record

Appendix B: JHH Pharmacy and Therapeutics Committee RDV Formulary Restriction and Order Review Process (12/11/2020)

Page 1: JHH Pharmacy and Therapeutics Committee RDV Formulary Restriction and Order Review Process (12/11/2020)

JOHNS HOPKINS
M E D I C I N E

MEMORANDUM   December 11, 2020

To: JHH Medical Staff
From: JHH Pharmacy and Therapeutics Committee
Re: Remdesivir Formulary Restriction and Order Review Process

Staff,

This memo is to inform you that JHH is implementing new formulary restriction criteria and ordering process for remdesivir on **Tuesday, December 15th**. These criteria were approved by the JHHS Formulary Management and Medication-Use Policy Committee (FMMPC) and reviewed by the COVID-19 Treatment Guidance Writing Group. This effort will ensure that remdesivir is initiated in patients meeting specific clinical criteria. The memo summarizes the revised formulary restriction criteria and the ordering process within Epic.

Overview:
- For initiation of remdesivir, patients must meet all clinical criteria within the formulary restriction in order to obtain medication.
- The medication order within Epic contains the formulary restriction criteria, and requires providers to answer a series of questions prior to signing the order.
- Once an order is placed for remdesivir, the pharmacist verifying the medication order must review the order to ensure the patient meets the clinical criteria.
    - If a prescriber is requesting use of remdesivir outside of the formulary restriction, the prescriber must contact the P&T Chair (Dr. Brent Petty) directly for review, preferably between 7 a.m. and 11 p.m.
- The use of remdesivir for pediatric patients is still under an Emergency Use Authorization (EUA) for those weighing 3.5 kg to less than 40 kg or those less than 12 years of age weighing at least 3.5 kg. See the last page for additional detail.

Formulary Restriction:
Patients must meet all of the following criteria to initiate remdesivir. Patients are limited to one course of 5 days of therapy.
- An RNA or antigen test indicating active COVID-19 infection (not serology)
- ≤10 days since COVID-19 symptoms began
- Presence of respiratory compromise at the time of clinical evaluation defined by one or more of the following:
    - $SaO_2 \le 94\%$ on room air for ≥ 1 hour
    - Requiring supplemental oxygen to maintain $SaO_2 > 94\%$ for ≥ 1 hour
    - Documented sustained RR ≥ 24 breaths per minute
- Not receiving mechanical ventilation or ECMO, unless these modalities were initiated for the first time within the past 24 hours
- ALT ≤ 10 times the upper limit of normal

Page 2: JHH Pharmacy and Therapeutics Committee RDV Formulary Restriction and Order Review Process (12/11/2020)

- If patients have an eGFR less than 30 mL/min, the attending physician will be required to enter a note indicating that the patient has been informed that use in patients with eGFR less than 30 mL/min is not recommended per the package label but the patient has agreed to receive remdesivir. This must be documented in the EHR. The smartphrase **.REMLESS30** can be used.
  - .REMLESS30:

    I am treating my patient who has documented COVID-19 infection with remdesivir because he/she meets the criteria set forth by JHHS for this therapy. The patient has an eGFR less than 30 mL/min. Wording in the FDA package insert notes that remdesivir is not recommended in patients with eGFR less than 30 mL/min. I believe that the benefits of treating this patient with remdesivir outweigh the potential harms because to date, there have not been reported renal or hepatic side effects associated with five days of remdesivir treatment in patients with an eGFR less than 30 mL/min. I will monitor my patient's renal and hepatic function while he/she is receiving remdesivir. I have discussed with the patient/legally authorized representative the benefits and risks of remdesivir therapy, including but not limited to the FDA package insert language. I have also counseled the patient/legally authorized representative on any potential alternative treatments. I have given the patient/legally authorized representative a chance to have all of his/her questions answered. The patient/legally authorized representative has elected to receive remdesivir therapy.

Pediatric Patients who fall under the EUA:
- The use of remdesivir for pediatric patients is still under an EUA for those weighing 3.5 kg to less than 40 kg or those less than 12 years of age weighing at least 3.5 kg. The JHHS clinical restriction criteria also apply.
  - Providers will be required to answer the above clinical questions verifying the patient meets JHH restriction criteria and EUA criteria.
  - **Providers must also answer all questions related to the EUA prior to signing order (in addition to the clinical questions):**

I have given the "Fact Sheet for Patients and Parents/Caregivers" to the patient/patient caregiver and informed the patient/patient caregiver of alternatives to remdesivir and that remdesivir is an unapproved drug that is authorized for use under EUA.

Yes No

All serious adverse events considered to be potentially related to remdesivir must be reported to MedWatch and Gilead within 7 days of the event. All medication errors and serious adverse events should also be reported through HERO

I agree to the requirement.

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Formulary Comments:
- The above criteria apply to all patients, including those with immune compromise, malignancy or history of solid organ transplant.
- According to the package label, remdesivir is not recommended in patients with eGFR < 30 mL/minute, but it is not listed in the package label as contraindicated. If a JHHS patient with eGFR < 30 mL/minute is ordered to receive remdesivir, there must be documentation in the medical record that the attending physician has informed the patient that the medication is not recommended per the package labeling and that the patient has agreed to receive remdesivir anyway, expecting the benefits to outweigh any risks.
- If ALT increases to > 10 times the upper limit of normal or the patient develops other signs or symptoms of hepatotoxicity, remdesivir must be discontinued.
- Remdesivir is a substrate of CYP3A4. At this time, no drug-drug interaction studies have been performed. Use caution when giving remdesivir with CYP3A4 inhibitors (e.g., azole antifungals) or inducers (e.g., rifampin).
- Patients who are transferred to JHHS from an outside hospital on remdesivir can complete their 5-day course of therapy.
- Patients well enough for discharge home can be discharged without completing their current course of remdesivir.

Allocation strategy outlined in the JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19 will be followed when demand exceeds supply.

Epic ordering:
- Providers are required to go through a series of questions ensuring patients meet all clinical criteria prior to signing the order.