# JHMI Clinical Recommendations for Pharmacologic Treatment of COVID-19

**Updated 7/7/2021 and replaces the version of June 9, 2021**; COVID-19 Treatment Guidance Writing Group of Johns Hopkins University and The Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

**New in the 7/7/2021 Update |** Go to current Writing Group recommendations

- The U.S. government has paused the distribution of bamlanivimab/etesevimab, and this combination is not recommended (more information).
- New data from a study of high-dose casirivimab/imdevimab in hospitalized patients (the REGN-COV2 arm of the RECOVERY study).

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# 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 to treat patients diagnosed with COVID-19.

- **Current approved JH 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**

- insideHopkins > Department of Hospital Epidemiology and Infection Control (intranet)
- VTE Prophylaxis for Symptomatic COVID Positive Patients (intranet or uCentral app)
- JHH and JHBMC Discharge Guidelines for COVID Positive Patients Still on COVID Isolation (intranet)
- Johns Hopkins Institute for Clinical and Translational Research: Current Approved Therapeutic Protocols for COVID-19
- 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 before symptom onset and extending to approximately 5 days after symptom onset.

**Symptomatic infection:** Headache, myalgia, and upper respiratory symptoms, including sore throat, are typical initially. They 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 bilateral ground-glass opacities in the lungs; lymphocytopenia is also commonly observed.[9,10] Patients with severe disease may become hypoxic and require high-flow oxygen support or mechanical ventilation to maintain oxygen saturation levels >92%.

The risk of progression to severe COVID-19 and hospitalization increases with the presence of specific 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 the cytochrome release syndrome (CRS) associated with chimeric antigen receptor T-cell therapy (CAR-T).[20-26] Patients may progress to multiorgan failure as a result of the cytokine-mediated hyperinflammation.[27]

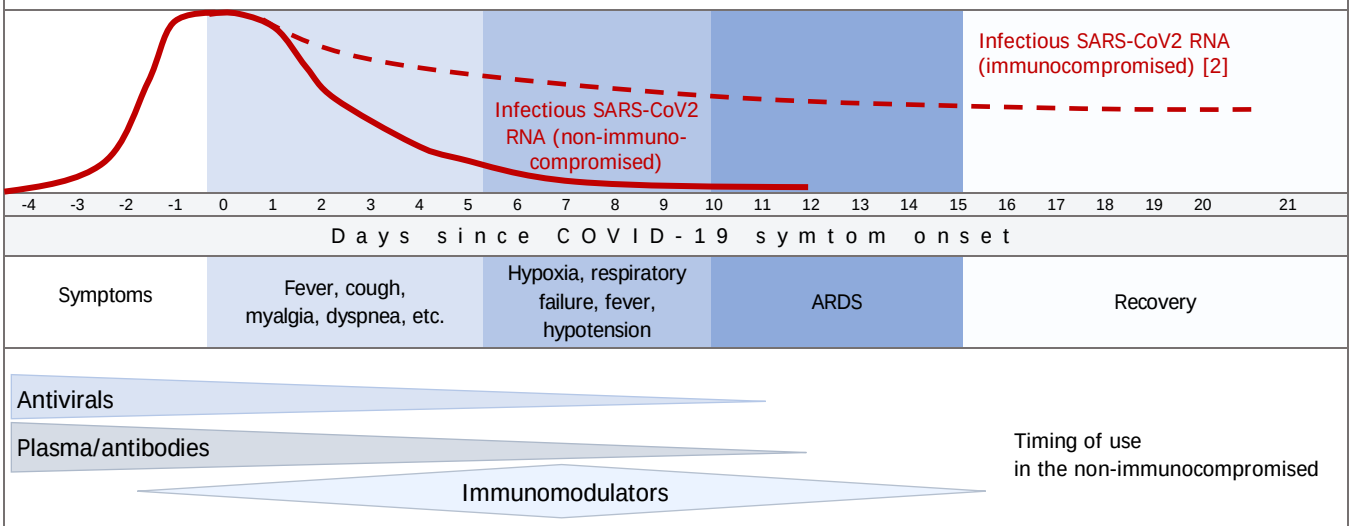
**Vascular disease:** Microvascular thrombosis and venous thromboembolism also occur with severe COVID-19.[28-30]

**Goals and optimal timing of treatment:** In this guidance, the timing for administration of pharmacologic agents is based on the type of medication and the potential for direct antiviral effect, modulation of an excessive inflammatory response, or a nonspecific adjuvant effect on the host, as illustrated in the figure below.

- **Outpatient treatment:** The primary goal of outpatient treatment is to limit disease progression, which requires treatment initiation early in the disease course, either before symptom onset or shortly thereafter.
- **Inpatient treatment:** The 2 therapeutic goals for inpatient treatment are limiting disease progression through antiviral activity and limiting COVID-19-related inflammation.

**Figure. Schematic of Clinical Course of Severe COVID-19**

Representation of SARS-CoV-2 RNA levels correlating with infectious replicating virus (shedding of non-infectious viral RNA may persist for a much longer time), common symptoms, and possible timing of therapeutics for the greatest benefit. Duration of symptoms and viral shedding may be prolonged in some patients who are substantially immunocompromised. Below, the red lines illustrate the typical trends for SARS-CoV2 RNA levels in individuals who are and are not immunocompromised. [1]




Notes:

1. Viral variants may have longer period of infectious virus, i.e., >10 days in normal hosts[2,4-6,31-33]
2. In the immunocompromised, variable duration, especially in severely immunocompromised (longer)

## III. Current Writing Group Recommendations for JHMI

Current writing group recommendations for pharmacologic treatment are summarized in Box 2, below. Links are provided to the sections of the document in which additional information and supporting evidence are 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 (RDV):** This writing group recommends that clinicians prescribe RDV to treat hospitalized patients with COVID-19 who meet the JHHS Formulary COVID Drug Approval Committee criteria (more information). Also see Box 4: Recommended Remdesivir Treatment for Immunocompromised Patients.
- ☑ **COVID-19 convalescent plasma:** Based on available evidence, if convalescent plasma is considered for use in a hospitalized patient with COVID-19 who is at higher risk for clinical progression, early treatment with a "high-titer" unit, based on cut-points defined by the U.S. Food and Drug Administration (FDA) for each assay, is advised--within 3 days (ideal) of symptom onset to 3 days after hospitalization (see below for additional parameters and more information).
- ☑ **Monoclonal antibodies active against SARS-CoV-2 (casirivimab/imdevimab and sotrovimab):** These medications are available for treatment of ambulatory patients with COVID-19 who are at risk of developing severe disease (more information).

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

- ☑ **Corticosteroids:** Dexamethasone is recommended for the treatment of COVID-19 in patients who have either a persistent need for noninvasive supplemental oxygen to maintain SaO2 ≥94% or who require mechanical ventilation (more information).
- ☑ **Baricitinib**: Baricitinib is recommended only for treatment of patients with severe COVID-19 who require oxygen supplementation and meet the criteria of the JHHS Formulary COVID-19 Drug Approval Committee, namely patients for whom dexamethasone is not advisable (more information).
- ☑ **Tocilizumab:** Tocilizumab may be considered for hospitalized patients receiving dexamethasone and require high-flow oxygen or are in their first 24-hours of intensive care for organ support, including mechanical ventilation. Patients who may benefit generally have elevated inflammatory markers (e.g., CRP). Interleukin-6 levels are not part of the assessment of tocilizumab eligibility. To prescribe tocilizumab, clinicians must secure approval from the JHHS Formulary COVID-19 Committee (more information).
- ☑ **Agents to avoid for treatment of COVID-19 outside of a clinical trial:** 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 the agents below are harmful when prescribed for the treatment of other conditions in patients with COVID-19 (more information).

  - ACE inhibitors or ARBs (initiation or d/c)
  - Azithromycin
  - Baloxavir marboxil
  - Colchicine
  - Darunavir/ritonavir
  - DAS 181
  - Famotidine
  - Favipiravir*
  - Fluvoxamine
  - Hydroxychloroquine
  - Indomethacin or other NSAIDs
  - Ivermectin
  - Lopinavir/ritonavir
  - Nitazoxanide
  - Oseltamivir
  - Ribavirin
  - Umifenovir*
  - Vitamin C
  - Vitamin D
  - Zinc

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**Abbreviations:** ACE, angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; eGFR, estimated glomerular filtration rate; EIND, emergency investigational new drug; 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

*Not FDA-approved or available for use in the United States

# 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 the introduction of exogenous antibodies (neutralizing monoclonal antibodies and convalescent plasma), and upregulation of the immune response (interferon).

## ☐ Remdesivir

Remdesivir (RDV) is an intravenous antiviral medication that has *in vitro* activity against SARS-CoV-2 and other coronaviruses.[34,35]

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 participants who were ready for discharge before completing 10 days of treatment. Through 28 days of observation following randomization, participants in the RDV arm had a median time to recovery of 10 days compared to 15 days among those in the placebo arm ($p<0.001$).[36] 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 participants 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 receiving 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.

A randomized clinical trial (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); exclusion criteria included mechanical ventilation or ECMO.[37] The study reported no difference in clinical outcomes based on treatment duration arm. On day 14, 60% of participants 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 participants compared to 17% of the 10-day arm participants 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. On day 11, there was a significant difference in clinical status in the 5-day RDV treatment group compared to the standard of care group.[38]

The SOLIDARITY study is a pragmatic, open-label RCT of RDV, hydroxychloroquine, lopinavir/ritonavir, and subcutaneous interferon beta 1a.[39] The study was conducted in 405 hospitals in 30 countries and depended on use of medications routinely available in each hospital. A total of 11,266 hospitalized adults were randomized to receive 10 days of RDV (2,750), or hydroxychloroquine (954), lopinavir/ritonavir (1,411), lopinavir/ritonavir plus interferon (651), interferon alone (1,412), or no study drug (4,088). Day 28 mortality was 12%. There was no reduction in death among those who received RDV compared to standard of care (risk ratio 0.95, $p=0.5$). There was also no difference in the need for mechanical ventilation or time to discharge. This study did not include clinical improvement assessments in comparison to the ACTT-1 study. 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 participants who received RDV compared to matched participants who did not.[40]

On October 22, 2020, the FDA-approved RDV for the treatment of adult and pediatric patients ≥12 years who require inpatient care for treatment of COVID-19.

**Who is likely to benefit from RDV treatment?** The ACTT-1 study reported no significant difference in RDV effect among study participants with ≤10 days or >10 days of symptoms. An RCT from China reported a trend toward improved outcomes among participants 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 oxygen via nasal cannula (95% confidence interval).

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.

**Adverse events:** Adverse events (from RDV or COVID-19) reported in clinical trials[37,41] 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[37,41] 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.[42] 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 participants discharged from the hospital and a higher proportion 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, it appears that a 5-day course of RDV treatment is the most reasonable approach for individuals with intact humoral immune function.

**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 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.[43]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 participants with an eGFR <30 mL/min/$m^2$ or receiving renal replacement therapy. Concerns with use in patients with kidney impairment include the lack of data on the pharmacokinetics of RDV in this population and the excipient sulfobutylether-β-cyclodextrin sodium salt (SBECD) in RDV. 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/$m^2$ unless the potential benefit outweighs the potential risk (see FDA > Healthcare Provider 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 endstage renal

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

disease (ESRD) on dialysis or a range of chronic kidney disease (CKD) stages who received RDV did not identify any increased risk of side effects or further renal impairment.[44] In addition, IV voriconazole, another medication that contains SBECD, has been extensively used and evaluated in patients with varying degrees of severe kidney disease and kidney impairment without evidence of harm.[45-51]

**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.

**Box 3: JHHS Formulary Management and Medication-Use Policy Committee Restriction for Remdesivir**

- **Formulary restriction**: The criteria defined here apply to all patients with COVID-19 within the first 10 days of illness, except for patients who are substantially immunocompromised, as defined in Box 4 below. Patients who are not substantially immunocompromised 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 respiratory rate (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
- Patients on concomitant baricitinib can receive a 10-day course of remdesivir.
- **Therapy of COVID-19 more than 14-days after onset:** Use is restricted to approval by the JHHS Formulary COVID Drug Approval Committee. Patients must meet all of the following criteria to use remdesivir. Information is based on limited information such as case reports.
  - Qualifying patients must have a severely immunocompromised illness or significant iatrogenic immunosuppression that may influence control of SARS-CoV-2 viral replication (such as chronic prednisone use >20 mg daily, rituximab within 6 months, CLL). See Box 4, below.
  - Patients must have evidence of potential ongoing viral infection (positive RT-PCR for SARS-CoV-2, fever, new pulmonary infiltrates, worsening organ dysfunction) >14 days after symptom onset
  - Alternative infectious explanations ruled out through testing or lack of response to antimicrobials
- **All courses are restricted to 5 days of therapy, an additional 5 days of therapy can be requested for immunocompromised patients. The additional 5 days must be approved by an ID attending currently on service at Johns Hopkins Hospital (Mann, Solo Mann, Transplant Teaching, Transplant Solo, Polk).**
  - This approval process is specific to JHH; the process specific to other JHHS hospitals can be found in Lexicomp.

**Box 3: JHHS Formulary Management and Medication-Use Policy Committee Restriction for Remdesivir**

- If remdesivir is approved, combination therapy with convalescent plasma or SARS-CoV-2 monoclonal antibody therapies could be considered.
- **Comments:**
  - The above criteria apply to all patients in the first 10 days of illness, except for patients who are substantially immunocompromised, as defined in Box 4 below.
  - The Guidance Committee does not view renal dysfunction as a contraindication to remdesivir therapy as there is no substantial evidence that the accumulated excipient poses risks, although the FDA-approved prescribing information 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 JHHS Formulary COVID-19 Committee review).
  - Patients well enough for discharge home can be discharged without completing their current course of remdesivir.

**RDV treatment for immunocompromised patients:** Among patients who have received solid organ or bone marrow transplants, have a hematologic malignancy (leukemia, lymphoma, myeloma), or are severely B-cell-depleted, SARS-CoV-2 replication may persist for weeks or months and contribute to morbidity and mortality.[31,32,52-55] This effect is analogous to other acute viral infections (e.g., influenza, norovirus, respiratory syncytial virus) in patients with substantial immunodeficiency.[56,57] Treatment with antiviral medications, such as RDV, may change the course of COVID disease in patients with persistent SARS-CoV-2 replication. Several case reports have suggested this, some using multiple 10-day courses of RDV,[52,53] in which use of this antiviral medication was temporally associated with clinical improvement and an increase in the cycle threshold (Ct) value.

A low Ct value from specific reverse transcription-polymerase chain reaction (RT-PCR) platforms may suggest ongoing viral replication.[52,58,59] Integrating Ct values into the clinical assessment may offer supportive evidence of ongoing SARS-CoV-2 replication causing disease (e.g. Ct ≤30 cycles).[52,59] In solid organ transplant recipients and others with severe immunodeficiency, it appears that productive SARS-CoV-2 viral infection may routinely extend to day 21, which is a longer duration than that observed in non-immunocompromised populations.[52,53] In some cases, the duration may be much longer than 21 days. The non-standardized surrogate (Ct value) is employed only because there is no routinely available clinical laboratory testing currently available to conclusively distinguish between ongoing replication and the presence of SARS-CoV-2 RNA without replication.

Although the optimal treatment duration in these patients has not been defined, antiviral treatment is appropriate when ongoing viral replication is suspected or confirmed. The presence or absence of SARS-CoV-2-specific antibodies is not relevant to the decision to use RDV in this patient population given the lack of evidence that this correlates specifically with protection from disease.

RDV therapy may be considered in combination with antiviral high-titer convalescent plasma or SARS-CoV-2 monoclonal antibody therapies or in patients previously treated with those agents. Of note, monoclonal anti-SARS-CoV-2 spike protein antibodies are authorized for use only in a non-hospital setting; an EIND is currently required for use in hospitalized patients (see information below for the accessing the product through this mechanism).

**Box 4: Remdesivir Treatment for Substantially Immunocompromised Patients**

- **Criteria:** Patients with substantial immunodeficiency as exemplified by, but not limited to, the following examples—solid organ or bone marrow transplant/hematopoietic stem cell transplant, hematologic malignancy (leukemia, lymphoma, myeloma), or severe B-cell-depletion (e.g., common variable immune deficiency [CVID], treatment with rituximab or other anti-CD20 monoclonal antibodies)—and who meet the following criteria are eligible to initiate or extend the course of RDV treatment beyond that recommended for patients who are not immunocompromised:
  - RNA or antigen test indicating active SARS-CoV-2 infection (not serology) *AND*
  - >14 days since COVID-19 symptom onset or first SARS-CoV-2 PCR, with evidence of potential ongoing viral infection (persistent symptoms consistent with COVID-19 OR SARS-CoV-2 RT-PCR with a cycle threshold of ≤30 cycles).* Current COVID-19-related symptoms are not necessary if there is laboratory evidence of ongoing replication.
- **Approval:** Local P&T chair approval is required if the first dose is started>14 days after symptom onset.
- **Duration:** All courses are restricted to 5 days of therapy.
- **Severely immunocompromised patients:** An additional 5 days of therapy can be requested for immunocompromised patients; the request must be approved by an infectious diseases service (ID) physician currently attending on a JHH hospital service (i.e., Mann, Solo Mann, Transplant Teaching, Transplant Solo, Polk, Tucker) or by an ID consultant at a JHHS hospital.
  - Beyond day 14, local P&T chair approval is required for first course of RDV.
  - An ID attending on service at JHH, or an ID Consultant at other JHHS hospitals may approve an additional 5-day course of RDV.
  - A third RDV 5-day course would require P&T chair approval.

*The SARS-CoV-2 RT-PCR cycle threshold (Ct) value is not an FDA-approved laboratory test and is not reported with clinical laboratory results. Test performance characteristics depend on multiple factors, including test platform, sample quality, and patient characteristics. Ct values must be interpreted within the general clinical context and generally with the assistance of clinical microbiology or ID expertise.

## ☐ 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, mumps, polio, measles, rabies, SARS-CoV-1, MERS-CoV, and Ebola.[60-64] 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.[64] 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 hospitalized participants with a median duration of 30 days.[65] The primary outcome, clinical improvement within 28 days, was similar in the 2 arms.
- An RCT from the Netherlands was halted early for futility.[66] At the time of enrollment, participants had experienced a median of 10 days of symptoms, and most had high levels of neutralizing antibodies, which may explain the reported similar overall outcomes between treatment and control groups.
- A placebo-controlled RCT from Argentina randomized 333 hospitalized patients with severe COVID-19 2:1 to convalescent plasma or placebo at a median of 8 days from the time of symptom onset.[67] Day 30 outcomes were similar between trial arms.
- Another placebo-controlled RCT from Argentina randomized 160 ambulatory patients age ≥75 years or 65 to 74 years with comorbidities with <48 hours of COVID-19 signs and symptoms 1:1 to convalescent plasma and placebo.[68] At day 15, more participants in the placebo arm (31%) compared to the convalescent plasma arm (16%) developed severe respiratory disease (p=0.02).

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 (among populations without humoral immunodeficiency).

Analyses 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 improved outcomes. The safety study identified a low risk of adverse events among 21,987 patients (see below). A mortality analysis included 35,322 participants with severe COVID-19 who were transfused between April 4 and July 4, 2020.[69] Lower mortality (7-day and 30-day) was reported in those 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 participants 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 those who received a low-titer unit (SARS-CoV-2 IgG S/Co ≤4.62). Further results from this retrospective study confirm the initial finding of improved outcomes among participants who received higher- rather than lower-titer convalescent plasma.[69] The study's limitations include the lack of a non-convalescent plasma comparator arm, potential prognostic differences between individuals transfused earlier and later, changes in clinical practice over time, and increased availability of high-titer units over time.

**Novel variants and convalescent plasma:** It is unclear whether novel variants will diminish any potential *in vivo* benefit of convalescent plasma. A small *in vitro* study reported a 15-fold decrease in the neutralization of a novel strain by plasma from an individual infected with an earlier SARS-CoV-2 strain.[70]

**Benefits and risks:** As noted above, the benefit is most likely to be achieved with high-titer convalescent plasma administered early, within 7 days of symptom onset (or possibly 3 days, as in one study that found a statistically significant benefit[68]) and, possibly, before hospitalization (although the FDA EUA does not currently allow administration of convalescent plasma in ambulatory patients).

**FDA EUA Links > Convalescent Plasma**

- Letter of Authorization (3/9/2021 reissue)
- Fact Sheet for Healthcare Providers
- Fact Sheet for Patients and Parents/Caregivers

The risks associated with the use of convalescent plasma include a very low risk of pathogen transmission (~1 in 2 million units),[64,71,72] allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.[71,72] A review of convalescent plasma therapy for severe or life-threatening COVID-19 in 5,000 participants in the U.S. found that SAEs at 4 hours post-

administration occurred in <1%.[73] An updated analysis of safety among 21,987 participants who received convalescent plasma in the U.S.as part of the FDA's EAP reported low rates of SAEs,[74] most of which were judged not to be related to the plasma. Venous thromboembolic disease was reported in <1%, cardiac events in 3%, and 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.

**FDA EUA:** Convalescent plasma had been accessible via one of the following mechanisms: a clinical trial, individual EIND, or EAP. The original FDA EUA was issued on August 23, 2020. The EUA was reissued on February 23, 2021, and was reissued again on March 9, 2021, to authorize the use of only high-titer convalescent plasma. The FDA granted a "grace period" that gives blood collection centers (e.g., American Red Cross, New York Blood Center, etc.) until June 2021 to label units.

The FDA EUA specifies the following:

- Only high-titer plasma units are authorized for administration. COVID-19 convalescent plasma must be tested for anti-SARS-CoV-2 antibodies with 1 of 9 available kits. However, blood banks have until June 2021 to comply with the required labeling of unit titers.
- Use should be initiated with the administration of 1 unit (200 mL). Additional convalescent plasma units may be administered based on a patient's clinical response.
- Physicians should consider the use of COVID-19 convalescent plasma among patients with impaired humoral immunity.
- Healthcare providers must make the FDA Fact Sheet for Patients and Parents/Caregivers available before use.

JHMI has issued consent to use convalescent plasma under the EUA (see Appendix C: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families).

**Procuring high-titer units:** JHH has "high-titer" plasma available for blood groups A, B, and O, which should be available for administration within about 1 hour of ordering. Blood group AB (<5% of the population) must be special-ordered (and will have a 2- to 3-hour delay if available; the delay may be longer during evenings or weekends). To request high-titer convalescent plasma at JHH:

- Complete the consent form specific to convalescent plasma; this can be found in "Forms on Demand."
- Complete the thawed order set in EPIC, and add "Emergency Use Authorization" in the comments section.
- Call the blood bank to inform them of the request for high-titer convalescent plasma. Units should be available in about 1 hour.
- If high-titer convalescent plasma is not available, a non-titer unit can be administered with a request post-infusion to have the blood bank sent an aliquot to the JHMI Immunology Lab. The lab will use the FDA-approved Euroimmune assay to measure the plasma titer. If the unit is low-titer, the clinician can then consider administration of a second unit. Second units are not routinely administered if the first unit is known to be high-titer.

**Box 5: 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, 1 outpatient clinical trials is enrolling at Johns Hopkins to study convalescent plasma treatment in cases of confirmed COVID-19 within 8 days of symptom onset (also see JH ICTR > Current Approved Therapeutic Protocols for COVID-19 for updates as they become available.
- **Use outside of a clinical trial:** High-titer convalescent plasma may be considered for the treatment of hospitalized patients who have mild COVID-19 symptoms, are at higher risk of clinical progression (≥65 years of age), and are within 3 days of symptom onset or 3 days of hospitalization or have underlying humoral immunodeficiency. Available clinical trial data demonstrated benefit when high-titer convalescent plasma was administered within 3 days of symptom onset in elderly patients with mild to moderate COVID-19.[57] Observational data suggest a possible benefit that wanes if high-titer convalescent plasma is received later than 3 days after hospitalization.[68,69] At present, as long as supply is available, the blood bank will use high-titer convalescent plasma except for blood type AB. Administration of subsequent units should be considered based on clinical response, per the FDA EUA, or the titer of units should be calculated post-infusion as described above. Available (low-quality) data do not support the use of convalescent plasma in other populations, including patients at low risk of clinical progression or with severe COVID-19.
- **Access:** Clinicians may contact the blood bank or their institution JHUcovidplasma@jhmi.edu. See the information above regarding the procurement of high-titer units at JHH.
- **Plasma donation:** Recovered patients who wish to be screened to donate convalescent plasma for clinical trial use at JHH should email JHUcovidplasma@jhmi.eduor contact the American Red Cross.

## 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 antibodies directed toward the SARS-CoV-2 spike protein.

**Not recommended: Bamlanivimab (LY-CoV555), bamlanivimab/etesevimab:** On June 25, 2021, the Assistant Secretary for Preparedness and Response and the FDA announced an immediate pause in the distribution of bamlanivimab and etesevimab for treatment of COVID-19. Also paused was distribution of etesevimab alone (for combination with existing supplies of bamlanivimab). A phase II clinical trial conducted before the emergence of variants of concern, 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.[75] Participants had confirmed COVID-19 and at least 1 COVID-19-related symptom but no need for supplemental oxygen. A significant reduction in emergency department visits and (predominantly) hospitalization was observed in the pooled mAb arms (1.6%) compared to the placebo arm (6.3%); the greatest difference was observed in the 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 symptoms to time of administration was 4 days. Adverse effects were similar in the 2 groups, and there were no serious adverse events in either group.

Multiple SARS-CoV-2 variants of concern, particularly the beta (B.1.351) and gamma (P.1) variants, have reduced susceptibility to bamlanivimab/etesevimab. As a result, the FDA recommends against use of bamlanivimab/etesevimab and has paused distribution.

**Casirivimab/imdevimab (REGN-COV2):** Preliminary analysis included 275 outpatients with NAT-confirmed COVID-19 who were enrolled and randomized 1:1:1 to receive a low or high dose of REGN-COV2 or placebo.[76] Before 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 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. The FDA updated the EUA on June 3, 2021 to authorize the following:

**FDA EUA Links >**

**Casirivimab/imdevimab:**

- FDA EUA Letter of Authorization (reissue 2/25/2021)
- Fact Sheet for Health Care Providers
- Fact Sheet for Patients, Parents, and Caregivers | Spanish
- Important Prescribing Information
- Frequently Asked Questions

**Sotrovimab:**

- EUA Letter of Authorization
- Fact Sheet for Health Care Providers
- Fact Sheet for Patients, Parents, and Caregivers
- Frequently Asked Questions

- Dose reduction to casirivimab 600 mg/imdevimab 600 mg
- Subcutaneous administration when intravenous infusion is not feasible or would delay treatment
- Use of a coformulated, single-vial product.

A REGN-COV2 RCT for hospitalized patients with varying illness severity was halted early due to an early concern that treatment may be more harmful than beneficial. In the subsequent REGN-COV2 arm of the RECOVERY trial, 9,785 hospitalized participants were randomized to receive either casirivimab 4,000 mg/ imdevimab 4,000mg or care as usual. Overall, there was no difference in mortality. However, among the 32% of participants who were seronegative for anti-spike protein antibodies, mortality was lower in the group that received REGN-COV2 (24%) than in the care-as-usual group (30%).[77] The current EUA does not authorize casirivimab/imdevimab for treatment of hospitalized patients, and it does not authorize use of the dose used in this study.

**Sotrovimab**: Interim analysis of results from an RCT of 583 non-hospitalized adults with mild COVID-19 symptoms for ≤5 days found an 85% reduction in the risk of hospitalization or death with sotrovimab compared to placebo.[78] Hospitalization or death occurred in 7% of placebo arm participants and 1% of sotrovimab arm participants. Sotrovimab retains activity against variants with reduced bamlanivimab/etesevimab neutralization. For more information, see the FDA EUA from May 26, 2021.

**Use of bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab:** These medications are not FDA-approved for the treatment of COVID-19; they can be accessed through clinical trials, the FDA EUAs for outpatients, and at JHH an EIND for specific high-risk patients (see hyperlinks above). Any use of these products in hospitalized patients requires an individual EIND application. 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). Because bamlanivimab/etesevimab has reduced activity against several variants of concern and use in Maryland may not continue, casirivimab/imdevimab is the favored product. Casirivimab/imdevimab maintains *in vitro* activity against the variants to which bamlanivimab/etesevimab has reduced activity.

**Outpatient treatment (per EUA):** Early clinical trial data suggest that patients with 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 supplemental 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:[79]

- BMI ≥35 kg/$m^2$
- CKD (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 1 of the following comorbidities:
  - BMI ≥85th percentile for their age and gender (based on growth charts from the 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

**Inpatient treatment with casirivimab/imdevimab (via the active EIND and IRB protocol):** Hospitalized patients with humoral immune impairment or other types of substantial immune deficiency may benefit from treatment with casirivimab/imdevimab, which can be accessed as an EIND. See Appendix B: Johns Hopkins Medicine Umbrella Protocol for Requests for Emergency Use of Casirivimab/Imdevimab and Remdesivir.

**Dosing and administration:** These medications are administered as 1-time intravenous infusions, which must be performed in a staffed setting that is that is equipped to monitor patients for 1 hour post-infusion and manage severe infusion reactions, such as anaphylaxis. Dose each as follows:

- **Bamlanivimab 700 mg and etesevimab 1,400 mg:** Mix together in a single infusion bag and infuse over at least 30 minutes. See FDA > Bamlanivimab and Etesevimab Fact Sheet for Health Care Providers.
- **Casirivimab 600 mg and imdevimab 600 mg:** Mix together in a single infusion bag and infuse over at least 60 minutes. The FDA authorized use of a coformulated, single-vial product in the 6/3/2021 EUA reissue, which also authorized subcutaneous administration. IV administration remains the strongly recommended route. See: FDA > Casirivimab and Imdevimab Fact Sheet for Health Care Providers (revised 6/21).
- **Sotrovimab 500 mg:** Infuse over at least 60 minutes. See FDA >Fact Sheet for Health Care Providers.

**Current local availability:** These agents are being administrated at the following State of Maryland locations: Baltimore Convention Center Field Hospital (see BCC COVID Infusion Center–Provider Referrals), University of Maryland Laurel 3-4-5 Alternative Care Site, Howard County General Hospital, Sibley Memorial Hospital, Tidal Health Peninsula, and Western Maryland Medical Center. Additional venues may be available in certain emergency departments, the JH Weinberg Infusion Center (available only for cancer patients), and Hatzalah of Baltimore (which offers infusions on Sundays). Agent selection is based on availability. See Maryland.gov > Resources for Health Care Professionals for additional locations and referral information.

### ☐ Interferon Beta-1b

Interferon (IFN) beta-1b is known to have an antiviral effect through immune response upregulation, 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.[80,81] 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.[82] Participants with <7 days of symptoms who received IFN beta-1b had a shorter time to reverse transcription PCR results for SARS-CoV-2 and symptom resolution.[82] IFN beta-1b likely provided most of the clinical benefit observed in this study; however, a placebo-controlled Phase III trial would help confirm findings.

## C. Immune Modulation

**Box 6: Recommendations for the Use of Immune Modulatory Agents to Treat COVID-19**

- ☑ **Corticosteroids:** Clinicians should not prescribe dexamethasone or other steroids to treat COVID-19 in 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 noninvasive 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,[83,84] the agents recommended for pregnant patients are prednisolone 40 mg daily by mouth or hydrocortisone 80 mg IV twice daily. Both of these medications have lower fetal concentrations due to 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.[85] In this study, there was a 35% reduction in mortality with dexamethasone among the subgroup receiving mechanical ventilation. There was also a reduction in mortality among those receiving supplemental oxygen and a trend toward increased mortality among the subgroup not receiving supplemental oxygen.
- ☑ **Baricitinib** can be used only with approval by the JHHS Formulary COVID Drug Approval Committee. The Committee membership includes Brent Petty (JHH), Amy Knight (JHBMC), Ayesha Kahlil (HCGH), Leo Rotello (SH), and Mark Abbruzzese (SMH). When seeking approval for use, the clinician should ensure that the patient meets the minimum criteria below:
  - Patients eligible for consideration must have confirmed COVID-19, meet EUA criteria, and require high-flow oxygen or noninvasive ventilation.
  - Patients are not eligible if they are taking dexamethasone or if they require mechanical ventilation.
  - The recommended regimen for patients approved for treatment is 14 days of baricitinib plus up to 10 days of RDV; however, both medications should be discontinued if the patient is discharged before completing treatment.
  - Clinicians may request an additional 5-day course of RDV (to equal 10 days total) if indicated.
- ☑ **Tocilizumab:** Its use may be considered for hospitalized patients receiving dexamethasone who require high-flow oxygen or are within the first 24 hours of intensive care for organ support, including mechanical ventilation. Patients who may benefit generally have elevated inflammatory markers (e.g., CRP). Since measurement of IL-6 levels were not part of the entry criteria or subgroup analysis in clinical

**Box 6: Recommendations for the Use of Immune Modulatory Agents to Treat COVID-19**

trials (EMPACTA, REMAP-CAP, RECOVERY) in which most patients also received dexamethasone, IL-6 values do not currently have a place in the assessment of tocilizumab eligibility. To prescribe tocilizumab, clinicians must secure approval from the JHHS Formulary COVID-19 Committee (more information).

☑ **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 or tocilizumab and lack of data to support the preference of any of these agents over tocilizumab or dexamethasone:

- Anti–GM-CSF mAb
- Anti-IL1
- Colchicine
- Convalescent plasma or serum-containing neutralizing antibodies
- Cyclosporine A
- Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)
- Intravenous immune globulin (IVIG)
- TNF-α inhibitors

## ☐ Corticosteroids

The recommendation for the use of dexamethasone is based on findings from the RECOVERY trial[85] and results of earlier studies of corticosteroid treatment for other types of viral pneumonia. The RECOVERY study's critical findings are that dexamethasone benefit was greatest among the most severely ill patients (i.e., receiving 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 participants with >7 days of symptoms but not among those 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. All patients hospitalized with COVID-19 were eligible to participate.[85] The 2,104 participants randomized to the dexamethasone arm received 6 mg by mouth 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. Participants receiving noninvasive supplemental 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 risk compared to standard of care was 0.65 (p=0.0003) for those on mechanical ventilation, 0.8 (p=0.002) for those receiving noninvasive supplemental oxygen, and 1.22 (p=0.1; a statistically non-significant increase in mortality) for participants who were not receiving supplemental oxygen. The benefit was reported only for participants who had >7 days of COVID-19-related symptoms in the age-adjusted analysis. In participants 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 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.

The GLUCOCOVID trial, a small open-label study that included 86 participants in the analysis, compared results in the group prescribed a glucocorticoid (methylprednisolone) with a group randomized to receive either glucocorticoid or no glucocorticoid. [86] Participants included in the analysis had ≥7 days of COVID-19 symptoms, pneumonia, hypoxia, elevated inflammatory markers, and were not 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/noninvasive ventilation found no significant difference by methylprednisolone use. In a per-protocol analysis, adjusting for age, methylprednisolone prescription was associated with a 24% reduction in the relative risk of the composite endpoint. Substantial limitations of this study are the lack of a randomized design and the primary benefit of delayed or reduced intensive care requirement.

**Meta-analysis of corticosteroid RCTs:** A meta-analysis that included 7 trials (1,703 patients, 59% of whom were participants in the RECOVERY trial) examined whether corticosteroids reduced 30-day mortality among critically ill patients with COVID-19.[87] Six of the 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 old, 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.[88]

## ☐ Targeted Immune Modulators

RCTs results have been reported for several immune modulators, including for those directed toward the IL-6 and IL-6 receptors (tocilizumab, sarilumab), the Janus Kinase pathway (JAK; baricitinib), IL-1 pathway (anakinra), and anti-GM-CSF (lenzilumab). These studies are discussed briefly here, with more detail provided below. In the EMPACTA,[89] REMAP-CAP,[90] and RECOVERY[91] studies of tocilizumab, in which most of the participants received corticosteroids, and all reported improvement in the primary outcome with tocilizumab. Earlier tocilizumab studies that did not include participants treated with corticosteroids failed to observe a difference in the primary outcome between tocilizumab and the comparator arm. Baricitinib reduced recovery time compared to placebo in the ACTT-2 study, primarily among participants receiving high-flow oxygen or noninvasive ventilation.[92] All participants received RDV; no data on corticosteroid were provided. The ACTT-4 study compared dexamethasone to baricitinib, both along with RDV. This study was halted early due to futility in demonstrating a difference between arms [see NIH closes enrollment in trial comparing COVID-19 treatment regimens]. The COV-BARRIER baricitinib study in which most participants received corticosteroids but <20% received RDV reported reduced mortality as a secondary endpoint.[93] Results of the LIVE-AIR study of the anti-GM-CSF monoclonal antibody lenzilumab reported lower survival without ventilation failure for lenzilumab than placebo; most participants received corticosteroids and RDV.[94]

No studies are available comparing targeted immunomodulatory agents, nor are studies available assessing the use of multiple targeted immunomodulatory agents. Because of both greater clinical experience and the number of RCTs involving tocilizumab, this writing group favors the use of tocilizumab when treatment with a targeted immunomodulatory agent is being considered.

**Tocilizumab with limited use (<20% at randomization) of concomitant corticosteroids:** A placebo-controlled RCT that included 243 participants with fever, pneumonia, and laboratory evidence of inflammation who were randomized to receive tocilizumab or placebo found no difference in clinical worsening or death at day 14 and day 28 endpoints.[95]

Two open-label RCTs that included participants with COVID-19 pneumonia or pneumonia and fever and elevated CRP reported no difference in survival at 28 days[96] or clinical progression at 14 days[97]; the later trial was halted early due to perceived futility. In a post-hoc analysis, the former trial reported lower 90-day mortality among the group with CRP >15 mg/dL who received tocilizumab compared to placebo (9 compared to 35%).[98]

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).[99,100]

**Tocilizumab with extensive use (>70% at randomization) of corticosteroids:** The Roche EMPACTA study of tocilizumab reported a reduction in mechanical ventilation in a double-blind RCT of 389 participants with COVID-19 pneumonia.[101] The hazard ratio of the primary outcome of progression to mechanical ventilation or death was 0.56 (p=0.04) among those 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 most significant contribution to the primary outcome was the time to progression of mechanical ventilation rather than just mechanical ventilation itself, raising questions about the clinical relevance of this finding. The incidence of infections was similar in both arms. A trial of sarilumab did not find a difference between arms in its primary or secondary endpoints.[102,103]

The REMAP-CAP study, an international adaptive clinical trial platform for testing multiple COVID-19 therapeutics, included tocilizumab or sarilumab compared to standard care (i.e., no placebo arm).[104] Participants were adults with COVID-19 admitted to an intensive care unit who were receiving respiratory or cardiovascular support in the form of high-flow oxygen, noninvasive or invasive mechanical ventilation or pressor drug therapies (19%); 77% received a corticosteroid. The median organ support-free days within 21 days of randomization were 10 for tocilizumab and 0 for standard care. Hospital mortality was 28% in the tocilizumab arm and 36% in the standard care arm. Both outcomes were significant based on Bayesian statistical analysis.

The RECOVERY trial, a multi-site factorial design RCT in the United Kingdom, included tocilizumab.[105] Participants were first randomized to one of the following: usual care, dexamethasone, lopinavir-ritonavir, hydroxychloroquine, azithromycin, or colchicine. Participants were subsequently considered for randomization to tocilizumab or no-tocilizumab if they had clinical progression as indicated by SpO2 <92% on room air, requiring oxygen therapy, or CRP ≥75 mg/L. A total of 4,116 participants were randomized 1:1 to tocilizumab or no-tocilizumab. Of these, 55% were receiving high-flow oxygen or invasive or noninvasive mechanical ventilation, and 45% were receiving supplemental oxygen via nasal cannula. The primary endpoint, 28-day mortality, occurred among 29% of the tocilizumab group and 33% of the no-tocilizumab group (p=0.007). In subgroup analysis, tocilizumab was found to be most effective when used concomitantly with corticosteroids and when given within 7 days of symptom onset.

An RCT conducted in Brazil enrolled 129 adult participants with COVID-19 to receive tocilizumab or standard care.[106] At enrollment, participants received supplemental oxygen or had received ≤24 hours of mechanical ventilation and had elevated inflammatory markers. The primary outcome, clinical status 15 days after enrollment, was not improved: in the tocilizumab arm, 28% of participants required mechanical ventilation or died compared with 20% in the standard care arm. The study was halted early out of concern for potential harm to those remaining in the tocilizumab arm as mortality at day 15 occurred in 11 (17%) of tocilizumab recipients and in only 2 (3%) of the standard of care/placebo group (OR 6.42, 95% CI 1.59-43.2).

Due to conflicting data, the risks and possible benefits of tocilizumab use should be weighed carefully and considered only in limited clinical circumstances, as described above.

**FDA EUA Links > Baricitinib/Remdesivir**
- Letter of Authorization
- Fact Sheet for Health Care Providers
- Fact Sheet for Patients, Parents, and Caregivers
- Frequently Asked Questions

**JAK inhibitors:** JAK inhibitors such as baricitinib, ruxolitinib, and fedratinib are FDA-approved for treatment of rheumatoid arthritis, myelofibrosis, or polycythemia vera and lead to the downregulation of TNF-α, IL-5, IL-6, and IL-1B.[107] Hence, these inhibitors may be useful against uncontrolled inflammation, such as that seen with COVID-19. The ACTT-2 study, which compared baricitinib and RDV to placebo and RDV, 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.[108] The ACTT-4 study compared the use of baricitinib to dexamethasone among individuals receiving RDV. The study was halted after enrolling approximately 1,000 participants due to a low chance of identifying a difference between arms [see NIH closes enrollment in trial comparing COVID-19 treatment regimens]. The lack of studies comparing baricitinib plus corticosteroids to just corticosteroids and the lack of difference between baricitinib and corticosteroids in the ACTT-4 study are why we are recommending the use of baricitinib only for patients unable to receive dexamethasone.

With 21% of participants from the U.S. and most of the others from Latin American countries, the COV-BARRIER study randomized 1,526 participants with elevated inflammatory markers (CRP, LDH, ferritin, or D-Dimer) to baricitinib or placebo; 96% received corticosteroids and 19% received RDV.[93] The primary outcome of progression to high-flow oxygen, noninvasive ventilation, invasive ventilation, ECMO, or death by 28 was not significantly different between groups (27.8% compared to 30.5% for placebo, p=0.2). All-cause mortality was lower in the baricitinib group: 8.1% compared to 13.1% (p=0.002). The difference in mortality between baricitinib and placebo was greatest among the subgroups that did not receive corticosteroids or RDV. These findings suggest that in settings where both RDV and dexamethasone are being used, baricitinib may have little effect on outcomes.

**GM-CSF inhibitors:** Lenzilumab neutralizes human GM-CSF, which is a cytokine upstream from IL-6. *In vitro* data suggest it may limit CRS.[109] The LIVE-AIR study compared lenzilumab to placebo among 520 participants, of whom 93% received corticosteroids and 72% received RDV.[94] The primary outcome of survival without ventilation failure occurred among 15.6% of lenzilumab and 22.1% of placebo participants (p<0.05); day 28 mortality occurred among 9.6% and 13.9% of lenzilumab and placebo participants, respectively. The mortality benefit appeared greatest for those <85 years of age and with CRP <15 mg/dL. The apparent greater benefit with less inflammation is in contrast to studies of tocilizumab suggesting greater benefit among participants with higher inflammatory markers.

**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.[110] 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.[111]

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

**Bruton's tyrosine kinase (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.[113] When used in an animal model of influenza, BTK inhibitors rescued mice from lethal lung injury.[114] 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.[115] A case series of 19 patients with COVID-19 treated with acalabrutinib suggested overall safety and reduced inflammatory markers.[116]

### ☐ Intravenous Immune Globulin (IVIG)

IVIG (non-convalescent) modulates immune response by interacting with antibodies and complement and blocking receptors on immune cells.[117] IVIG has been used to treat multiple conditions, including SARS and COVID-19, to control pathogenic inflammation. [118] A case series of 3 patients reported using IVIG at the point of clinical deterioration and presumed shift to cytokine dysregulation.[119] 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

**Box 7: 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 to treat other conditions in patients with COVID-19.

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), either initiation or discontinuation of use
- Aspirin
- Azithromycin
- Baloxavir marboxil
- Colchicine
- Darunavir/ritonavir
- DAS 181
- 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

| **Box 7: Recommendations for Agents to Avoid as Treatment for COVID-19 Specifically** |
| --- |
| *Use of HCQ for treatment or prophylaxis of COVID-19 is prohibited at JHHS unless it is part of a clinical trial. Patients who may have been prescribed HCQ for prophylaxis as an outpatient should not continue therapy for prophylaxis as an inpatient unless part of a clinical trial. |

For the agents listed above, there is no plausible evidence of or 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.[120] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression,[121] 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.[122] The best evidence suggests similar or improved outcomes among people on chronic ACE or ARB therapy who develop COVID-19.[123]

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.

**Aspirin:** Aspirin has a potential benefit in COVID-19 through its antithrombotic activity. A retrospective record review from multiple hospitals in the United States was used to compare 98 inpatients with COVID-19 who received aspirin to 314 who did not receive aspirin.[124] In an adjusted analysis, patients who received aspirin were less likely to require mechanical ventilation. Although the authors sought to adjust for multiple factors, the nature of this study cannot rule out the possibility that the association between aspirin and less mechanical ventilation was a result of confounding.

**Azithromycin:** Dosed as 500 mg daily for 3 days did not improve outcomes in 540 participants randomized to receive this medication in an adaptive trial.[125] 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.[126] No clinical efficacy was found in a study of azithromycin against MERS-CoV.[127]

**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.

**Colchicine:** Colchicine has been of interest for the management of COVID-19 due to its anti-inflammatory properties. A small RCT of 72 hospitalized participants reported a more rapid time to discontinuation of supplemental oxygen among participants who received 10 days of treatment with colchicine (4.0 days to O2 discontinuation) compared to placebo (6.5 days).[128] Another RCT, with 4,488 ambulatory COVID-19 patients, compared 30 days of colchicine treatment to placebo and found no substantial difference in the primary endpoint of death or hospitalization within 30 days of randomization, with 4.7% in the colchicine arm and 5.8% in the placebo arm meeting that composite endpoint.[129]

**Darunavir/ritonavir (DRV/RTV):** An *in vitro* study of DRV/RTV and RDV against SARS-CoV-2 reported no activity for DRV/RTV compared to potent activity for RDV.[130] 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.[130]

**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 viruses' ability 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.[131] 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.[132] 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 the possible value of this agent in treating COVID-19, and a trial of high-dose intravenous famotidine for COVID-19 is underway.[133]

**Favipiravir**: This inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.[134,135] 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.[135] 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.[134] 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):** HCQ's *in vitro* activity against SARS-CoV-2 and some other viruses[136,137] has not translated into efficacy in the treatment of any viral infection, and this writing group recommends against off-label use of HCQ for the treatment of COVID-19. The *in vitro* activity has not translated into a difference in clinical outcomes in placebo-controlled RCTs or matched cohort studies.[138,139] Multiple RCTs, including those sponsored by the NIH, have been halted because of the futility of HCQ treatment or under-enrollment.[140-143]

Mortality may have been increased with HCQ; however, study limitations preclude 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.[144]

**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*.[145] 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.[146] 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.[147] 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.[148-152] The largest RCT, which included 400 participants

with mild disease and <7 days of symptoms, reported no difference in time to symptom resolution between participants who received 5 days of ivermectin (300 ug/kg body weight/day) compared to those who received placebo.[153] A small RCT of 72 participants in 3 arms reported no difference in primary outcomes between study arms but reported more rapid clearance of viral RNA in the ivermectin arms.[154] A study conducted in Iraq among 118 participants with mild to severe COVID-19 compared 2 or 3 days of ivermectin plus doxycycline to standard therapy.[152] The time to recovery was 10.6 days in the ivermectin arm compared to 17.9 in the standard therapy arm ($p<0.05$). A (non-randomized) study conducted in Bangladesh compared 72 participants hospitalized with mild COVID-19 who received either 5 days of ivermectin, 5 days of ivermectin plus doxycycline, or standard treatment.[154] There was no difference in symptom resolution between study arms. Additional retrospective and prospective studies have been summarized in a systematic review (preprint).[150]

**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).[155] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[156] 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.[157] 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.[158] 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.[159]

**Nitazoxanide:** This agent has been tested *in vitro* against MERS-CoV and SARS-CoV-2 and found to have activity.[160] 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.[161]

**RBV:** In a systematic review, RBV was not found to be beneficial against SARS-CoV-1.[162] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[163]

**Umifenovir:** This agent was routinely used in China to treat patients with COVID-19.[164] There are no data to support its effectiveness. This drug is not approved by the FDA and is not available in the United States.

**Vitamin C:** Based on a prospective randomized trial of intravenous vitamin C in patients with sepsis and ARDS, vitamin C has been suggested as a treatment option for COVID-19.[165] 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.[166] 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.[167] 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. However, an RCT of 240 patients randomized to a single administration of 200,000 IU of vitamin $D_3$ found no difference in the 7-day hospital length of stay in either arm.[168] Clinical trials have found that patients with other diseases who had vitamin D levels <20 ng/mL benefited from

supplementation; however, in this COVID-19 study, no benefit was found in the subset with levels less than 20 ng/mL.

**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.[169]

# 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 8: COVID-19 Pharmacologic Treatment Guidance Writing Group**

- **Chair:** Paul G. Auwaerter, MD, MBA, Clinical Director, Division of Infectious Diseases; Professor of Medicine
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  - 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; Associate Professor of Medicine and Oncology
  - 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

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: Comparison of Selected Studies of Targeted Immunosuppression

**Table A-1: Comparison of Selected Studies of Targeted Immunosuppression**

| Trial | COV-BARRIER [1] | ACTT-2 [2] | LIVE-AIR [3] | EMPACTA [4] | REMAP-CAP [5] | RECOVERY [6] |
|---|---|---|---|---|---|---|
| **Type** | RCT: DB, PBO-C | RCT: DB, PBO-C | RCT: DB, PBO-C | RCT: DB, PBO-C | Multifactorial, adaptive trial | RCT: Open-label |
| **Drug** | BARI 4 mg/day (N=764) v. PBO (n=761) | BARI 4 mg/day + RDV (n=515) v. PBO + RDV (n=518) | Lenzilumab 1,800 mg/day (n=261) v. PBO (n=259) | TOCI (n=249) v. PBO (n=128) | TOCI (n=353), SARI (n=48), SOC (n=402) | TOCI (n=2,022) v. SOC (n=2,094) |
| **Number: Population** | 1,525: hospitalized; no ICU; receiving SOC | 1,033: hospitalized; COVID-19 pneumonia, any | 520: hospitalized; with O2 need; no IMV | 389: hospitalized; COVID-19 pneumonia; no NIV or MV | 803 hospitalized w/in 24 hours of ICU organ support (high-flow O2, MV) | 4,116: hospitalized; hypoxia and CRP ≥75 mg/L |
| **COVID symptom duration** | • 17% <7 days (median)<br>• 83% ≥7 days (median) | 8.5 days (median) | No data; 2 hospital days before enrollment (median) | 8 days (median) | No data; 1.2 hospital days before enrollment (median) | • 9 days TOCI (mean)<br>• 10 days SOC (mean) |
| **Sites (% U.S.)** | Multinational (21%) | Multinational (82%) | Multinational (85%) | Multinational (80%) | Multinational (0%) | United Kingdom (0%) |
| **Steroid or RDV use** | • CS: 79%<br>• RDV: 18.9% | No data | • CS: 94%<br>• RDV: 72%<br>• CS + RDV: 69% | • CS: 80% TOCI; 87% PBO<br>• RDV: 52% TOCI; 5% PBO | • CS: 93% (after 6/17/20)<br>• RDV: 31% | CS: 74%<br>RDV: 27% |
| **Primary outcome** | Respiratory progression or death: 28% BARI v. 31% PBO (OR 0.85; 95% CI 0.67-1.08) | Time to recovery: 7 days BARI/RDV v. 8 days PBO/RDV (RR 1.16; 95% CI 1.01-1.32) | SWOV 54% mITT (HR 1.54; 95% CI 1.02-2.31) | 28-day IMV or death: 12% TOCI v. 19% PBO (HR 0.56; 95% CI 0.33-0.97) | Organ support-free days (median): 10 days TOCI v. 11 days SARI v. 0 days SOC (OR 1.64; 95% CI 1.25-2.14) | 28-day mortality: 31% TOCI v. 35% SOC (RR 0.85; 95% CI 0.76-0.94) |
| **Secondary outcome** | 38% reduction in 28-day all-cause mortality: 8% BARI v. 13% PBO (HR 0.57; 95% CI 0.41-0.78) | Multiple | • Decreased need for IMV, ECMO<br>• Decreased mortality in participants <85 years old with CRP <150 mg/L (OR 0.32; 95% CI 0.15-0.65) | Median time to clinical failure could not be estimated (HR 0.55, 95% CI 0.33-0.93) | • Improved 90-day survival for TOCI + SARI pooled (HR 1.61; 95% CI 1.25-2.08)<br>• In-hospital mortality 27% TOCI v. 22% SARI v. 36% control | 28-day hospital discharge: 57% TOCI v. 50% SOC (RR 1.22; 1.12-1.33) |
| **Comments** | Did not meet primary endpoint | • Time to recovery with high-flow O2 or NIV: 10 days BARI/RDV v. 18 days PBO/RDV (RR 1.51; 95% CI 1.10-2.08)<br>• 28-day mortality: 5% BARI/RDV v. 8% PBO/RDV (HR 0.65; 95% CI 0.39-1.09)<br>• SAE: 16% BARI/RDV v. 21% PBO/RDV | 92% SWOV reduction with CS + RDV (1.92; 1.20-3.07) | • Site-selection focused on inclusion of high-risk and minority populations<br>• SAE: 15% TOCI; 20% PBO<br>• No mortality difference | — | Survival and clinical improvement seen regardless of clinical stage |

**Table A-1: Comparison of Selected Studies of Targeted Immunosuppression**

**Abbreviations:** BARI, baricitinib; CI, confidence interval; CRP, C-reactive protein; CS, corticosteroids; DB, double-blind; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICU, intensive care unit; IMV, invasive mechanical ventilation; mITT, modified intention-to-treat; MV, mechanical ventilation; NIV, noninvasive ventilation; O2, oxygen; OR, odds ratio; PBO, placebo; PBO-C, placebo-controlled; RCT, randomized clinical trial; RDV, remdesivir; RR, risk ratio; SAE, serious adverse event; SARI, sarilumab; SOC, standard of care; SWOV, survival without ventilation; TOCI, tocilizumab.

**References:**

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# Appendix B: Johns Hopkins Medicine Umbrella Protocol for Requests for Emergency Use of Casirivimab/Imdevimab and Remdesivir

**Purpose:** The purpose of this umbrella protocol is to provide a single application to the Johns Hopkins Medicine Institutional Review Board (JHM IRB) for clinicians to request emergency use of casirivimab/imdevimab and off-label use of remdesivir to treat hospitalized patients with COVID-19. Use of this umbrella protocol will allow treating clinicians to submit just 1 IRB application per patient. However, the treating clinician will have to submit a change in research to the IRB and add all applicable documentation pertaining to a specific patient/request.

the preferred process is to receive approval of a "change in research" by the JHM IRB before initiating treatment. However, if a patient's condition precludes delay, the "change in research" must be submitted to the IRB within 5 days of treatment initiation.

**Steps for submitting the change in research:**

1. Submit the approved FDA documentation and sponsor approval.
2. Send an email notification of the request to the Johns Hopkins IRB (jhmeirb@jh.edu).
   a. Copy Ken Borst, Associate Director of Operations (kborst1@jhmi.edu).
   b. Use the subject line "IRB00284507 Emergency Use Request."
3. Contact umbrella protocol principal investigator Dr. Veronica Dioverti (mdiover1@jhmi.edu), who must submit the change in research through the IRB system.
   a. Request the approved treatment protocol/plan and consent form.
   b. You will be listed as a study team member on the IRB application.
4. Create a change in research via further study action in the IRB system.
   a. Section 1, item 1 of the change in research (CIR): Select the boxes next to "Drugs" and "Other".
   b. Section 1, item 3 of the CIR: Describe the documents that you have uploaded and their location, and confirm that you obtained sponsor approval. Generally, this will be limited to section 21 (Drugs) and section 20 (Supplemental Study Documents).
   c. Section 21 (Drugs), item 8: Create a new entry for the drug (REGN-COV), then answer all items that appear in a sub-box, thereby uploading the FDA-approved documentation, the Investigator Brochure, and the Investigational Drug Data Sheet. The link to the Investigational Drug Data Sheet is found here: https://www.hopkinsmedicine.org/institutional_review_board/forms/
   d. Section 20 (Supplemental Study Documents), item 2: Upload a clinical summary for the patient. If treatment was administered prior to the CIR submission, include the patient's current condition in the summary.
5. Once Dr. Dioverti has formally submitted the CIR, contact the JHM IRB and Ken Borst again to notify them of the submission.

# Appendix C: Johns Hopkins Medicine Investigational COVID-19 Convalescent Plasma: A Guide for Patients & Families (9/3/2020)

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

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

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

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

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

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

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

| Risks of Administration Vary, but Include: | Steps Taken to Reduce the Risk May Include: |
|---|---|
| **Transfusion Reaction: (less than 5%)**<br>• Fever, itching and hives are the most common mild symptoms<br>• Low blood pressure, difficulty breathing, and organ injury are more serious but also much less common | • Before being given,<br>  ○ except in life-threatening emergencies, donated plasma is matched with your blood type<br>  ○ you may be given medicine<br>• You will be monitored for any symptoms and the administration will be stopped if necessary |
| **Infection: (less than 0.1%)**<br>• Bacteria<br>• Viruses<br>• Parasites<br>• 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. |

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

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

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

JOHNS HOPKINS MEDICINE

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 MEDICINE

**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)*

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