JHMI Clinical Recommendations for Pharmacologic Treatment of COVID-19

Updated 1/13/2022 Update and replaces the version of 1/07/2022; COVID-19 Treatment Guidance Writing Group of Johns Hopkins University and The Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

Box 1: New in the 1/13/2022 Update
• Table 1: Summary JHMI Recommendations for Inpatient Pharmacologic COVID-19 Treatment updated to include ordering information for remdesivir (RDV) 3-day dosing and prioritization criteria for sotrovimab. • Table 2: Summary JHMI Recommendations for Ambulatory Pharmacologic COVID-19 Treatment updated to include limitations on RDV use and ordering information for molnupiravir, nirmatrelvir/ritonavir, and sotrovimab. • Box 3: JHHS Formulary Management and Medication-Use Policy Committee Restriction for Inpatient Use of Remdesivir: Criteria for inpatient 3-day RDV course for immunocompetent patients with mild to moderate COVID-19 hospitalized for reasons other than COVID-19.

Contents

I. Current Writing Group Recommendations for JHMI

Table 1: Summary JHMI Recommendations for Inpatient Pharmacologic COVID-19 Treatment

For treatment of solid organ or bone marrow transplants recipients, consult with an infectious diseases clinician

Agent	Criteria for Authorized Use	Comments
Patients Early in COVID-19 Disease Course		
Remdesivir	• ≤10 days symptoms • Supplemental O_2 required • ECMO or mechanical ventilation ≤24 hours only	• May consider use in pregnancy.
Molnupiravir [a] (Not currently available within JHHS)	• ≤5 days symptoms • ≥18 years old • Non-severe, non-critical COVID • At risk for severe COVID-19 [b] • Unvaccinated or unlikely to respond to vaccine • Ineligible if O_2 required for COVID-19	• Teratogenicity and mutagenicity concerns in pregnancy.
Nirmatrelvir/ ritonavir [a] (Not currently available within JHHS)	• ≤5 days symptoms • ≥12 years old • Non-severe, non-critical COVID • At risk for severe COVID-19 [b] • Unvaccinated or unlikely to respond to vaccine • Ineligible if O_2 required for COVID-19	• Substantial drug-drug interactions with ritonavir up to 2 weeks after the last dose; consult with a clinical pharmacist as necessary. • No data on use in pregnancy.
Limited to Hospitalized Patients With Early Nosocomial COVID-19 and No Supplemental Oxygen Requirement [c]		
Remdesivir	• ≤7 days new symptoms consistent with COVID-19 (fevers, chills, dyspnea, cough, pharyngitis, myalgia, diarrhea, vomiting, or dysgeusia or anosmia) • At risk for severe COVID-19 [b] • Meets EUA sotrovimab criteria but mAb unavailable or directed to ambulatory use • Ineligible if O_2 required for COVID-19	• Order through EPIC and must meet criteria; see Table 3 for full description. • Administered as a 3-day infusion (200 mg IV day 1, then 100 mg IV day 2 and day 3). • May consider use in pregnancy. • Patients are not to be admitted solely for RDV infusion. • If a patient develops an O_2 requirement, additional RDV approval is required via a process determined by each hospital; see Table 3 notes for details.
Sotrovimab (Supply is limited)	• ≤7 days symptoms • At risk for severe COVID-19 [b] • Ineligible if O_2 required for COVID-19	• At JHMI, use is limited to highest-risk populations. • MD DOH manages outpatient distribution to health systems. • May consider use in pregnancy.
Bamlanivimab/ etesevimab (Not currently in use)	• ≤10 days symptoms • At risk for severe COVID-19 [b] • Ineligible if O_2 required for COVID-19	• Not effective against Omicron variant. • May consider use in pregnancy.
Casirivimab/ imdevimab (Not currently in use)	• ≤10 days symptoms • At risk for severe COVID-19 [b] • Ineligible if O_2 required for COVID-19.	• Not effective against Omicron variant. • May consider use in pregnancy.
Hospitalized With Progressive COVID-19 Disease		
Dexamethasone	• Supplemental O_2 required • Intensive care use allowed	• Use in pregnant patients same as in the non-pregnant.
Tocilizumab	• Supplemental O_2 required, high flow OR intensive care ≤24 hours • CRP >7.5 if immunocompetent	• Use in combination with dexamethasone. • P&T committee chair or designee approval required

Table 1: Summary JHMI Recommendations for Inpatient Pharmacologic COVID-19 Treatment *For treatment of solid organ or bone marrow transplants recipients, consult with an infectious diseases clinician*		
Agent	**Criteria for Authorized Use**	**Comments**
		• For immunocompromised patients, P&T approval does not require CRP. • May consider use in pregnancy.
Baricitinib (If tocilizumab is unavailable)	• Supplemental O_2 required • Intensive care ≤24 hours allowed	• P&T committee chair or designee approval required. • Animal study concerns for use in pregnancy.
Limited to Patients With Compromised Immune Status		
Convalescent plasma (Currently unavailable)	• Immunosuppressed or receiving immunosuppressive therapy • Response may be better early in disease. • Any O_2 requirement allowed	• High titer required to neutralize Omicron variant. • May consider use in pregnancy.
Remdesivir	• Immunocompromised [d] • Any O_2 requirement allowed • Intensive care use allowed	• ID attending approval required, see Table 3 notes for details. • May consider use in pregnancy.

Abbreviations: CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; EUA, Emergency Use Authorization; ID, infectious diseases; ID, infectious diseases; IV, intravenous; JHHS, Johns Hopkins Health System; JHMI, Johns Hopkins Medical Institutions; MD DOH, Maryland Department of Health; O_2, oxygen; PO, by mouth; P&T, Pharmacy & Therapeutics Committee; RDV, remdesivir

Notes:

a. If supply is available and agent is on formulary, it may be administered to hospitalized patients who do not have severe or critical COVID-19.

b. Meets at least 1 of the following criteria: body mass index ≥25 kg/m2; chronic kidney disease; diabetes; pregnancy; immunosuppressive disease with ongoing immune deficiency; currently receiving immunosuppressive treatment; cardiovascular disease or hypertension; chronic lung disease; sickle cell disease; neurodevelopmental disorders (e.g., cerebral palsy) or conditions conferring medical complexity, including severe congenital abnormalities, genetic or metabolic syndromes; medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive-pressure ventilation requirement not related to COVID-19)

c. Patients admitted for conditions other than COVID-19 with nosocomial SARS-CoV-2 infection or incidental COVID-19 diagnosis.

d. Immunodeficient, as exemplified by but not limited to the following examples: Solid organ or bone marrow transplant/hematopoietic stem cell transplant; hematologic malignancy, such as leukemia, lymphoma, myeloma, or severe B-cell depletion (e.g., common variable immune deficiency [CVID]); receiving rituximab or other anti-CD20-based treatment). Patients must have ≤21 days since COVID-19 symptom onset or first SARS-CoV-2 PCR (current COVID-19–related symptoms are not necessary), or if >21 days since COVID-19 symptom onset or first SARS-CoV-2 PCR, the patient must have a SARS-CoV-2 RT-PCR with a cycle threshold of ≤30 cycles (if cycle threshold is available at the site; if not available, the patient must have other evidence of ongoing viral infection).

1/13/2022

Table 2: Summary JHMI Recommendations for Ambulatory Pharmacologic COVID-19 Treatment

For treatment of solid organ or bone marrow transplants recipients, consult with an infectious diseases clinician

Agent	Authorized Use	Comments
Patients Early in COVID-19 Disease Course		
Remdesivir (If mAb is not available)	• ≤7 days symptoms • At risk for severe COVID-19 [a]	• Administered as 3-day infusion. • JH infusion capability is limited and sotrovimab is prioritized. • May consider use in pregnancy. • May be subject to insurance approval.
Molnupiravir (Available through dedicated retail pharmacies)	• ≤5 days symptoms • ≥18 years old • Unvaccinated or unlikely to respond to vaccine • At risk for severe COVID-19 [a]	• For MD pharmacies, see MedChi Coronavirus Resource Center Oral Therapeutics. • For pharmacies outside of MD, see COVID-19 Public Therapeutic Locator [this page can be accessed only within the JHMI network]. • Teratogenicity and mutagenicity concerns for use in pregnancy.
Nirmatrelvir/ritonavir (Available through dedicated retail pharmacies)	• ≤5 days symptoms • ≥12 years old • Unvaccinated or unlikely to respond to vaccine • At risk for severe COVID-19 [a]	• Substantial drug-drug interactions with ritonavir up to 2 weeks after the last dose; consult with a clinical pharmacist as necessary. • For MD pharmacies, see MedChi Coronavirus Resource Center Oral Therapeutics. • For pharmacies outside of MD, see COVID-19 Public Therapeutic Locator [this page can be accessed only within the JHMI network]. • No data on use in pregnancy.
Sotrovimab (Limited availability)	• ≤10 days symptoms • At risk for severe COVID-19 [a]	• Infusion site determines patient priority based on agent availability. • JHH infusion (Park) or JH Homecare limited availability; Kimmel Biomode for oncology patients only. • For Baltimore City details, see UMMS BCCFH COVID Task Force Infusion Center for details. • For State of MD details, see MD DOH Monoclonal Antibody Treatment Administration Locations for COVID-19. • May consider use in pregnancy.
Bamlanivimab/ etesevimab (Not currently in use)	• ≤10 days symptoms • At risk for severe COVID-19 [a]	• Not effective against Omicron variant. • May consider use in pregnancy.
Casirivimab/ imdevimab (Not currently in use)	• ≤10 days symptoms • At risk for severe COVID-19 [a]	• Not effective against Omicron variant • May consider use in pregnancy.
Fluvoxamine (Timely administration of antiviral or mAb is not possible)	• ≤7 days of symptoms	• Potential fetal harm in the third trimester if used in pregnancy.
Limited to Patients With Compromised Immune Status [b]		
Convalescent plasma (Currently unavailable)	• Response may be better early in disease.	• High titer required to neutralize Omicron. • May consider use in pregnancy.

Abbreviations: BCCFH, Baltimore Convention Center Field Hospital; ECMO, extracorporeal membrane oxygenation; ID, infectious diseases; IV, intravenous; MD DOH, Maryland Department of Health; O_2, oxygen; PO, by mouth; P&T, Pharmacy & Therapeutics Committee; UMMS, University of Maryland Medical System

Notes:

a. Meets at least 1 of the following criteria: body mass index ≥25 kg/m2; chronic kidney disease; diabetes; pregnancy; immunosuppressive disease with ongoing immune deficiency; currently receiving immunosuppressive treatment; cardiovascular disease or hypertension; chronic lung disease; sickle cell disease; neurodevelopmental disorders (e.g., cerebral palsy) or conditions conferring medical complexity, including severe congenital abnormalities, genetic or metabolic syndromes; medical-

Table 2: Summary JHMI Recommendations for Ambulatory Pharmacologic COVID-19 Treatment *For treatment of solid organ or bone marrow transplants recipients, consult with an infectious diseases clinician*		
Agent	**Authorized Use**	**Comments**
related technological dependence (e.g., tracheostomy, gastrostomy, positive-pressure ventilation requirement not related to COVID-19) b. Immunodeficient, as exemplified by but not limited to the following examples: Solid organ or bone marrow transplant/hematopoietic stem cell transplant; hematologic malignancy, such as leukemia, lymphoma, myeloma, or severe B-cell depletion (e.g., common variable immune deficiency [CVID]); receiving rituximab or other anti-CD20-based treatment). 1/13/2022		

II. 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 JHMI therapeutic protocols for COVID-19:** See Johns Hopkins Institute for Clinical and Translational Research: Current Approved Therapeutic Protocols for COVID-19
- **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 National Institutes of Health (NIH) Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.

Box 2: Resources for Johns Hopkins Clinicians
• Department of Hospital Epidemiology and Infection Control COVID-19 Clinical Resources (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 ICTR: Current Approved Therapeutic Protocols for COVID-19 • JHMI Lab Testing Guidance for Symptomatic COVID-19 Inpatients (intranet)

III. 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 disease 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 by fever, cough, diarrhea, and anosmia a few days later. 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]

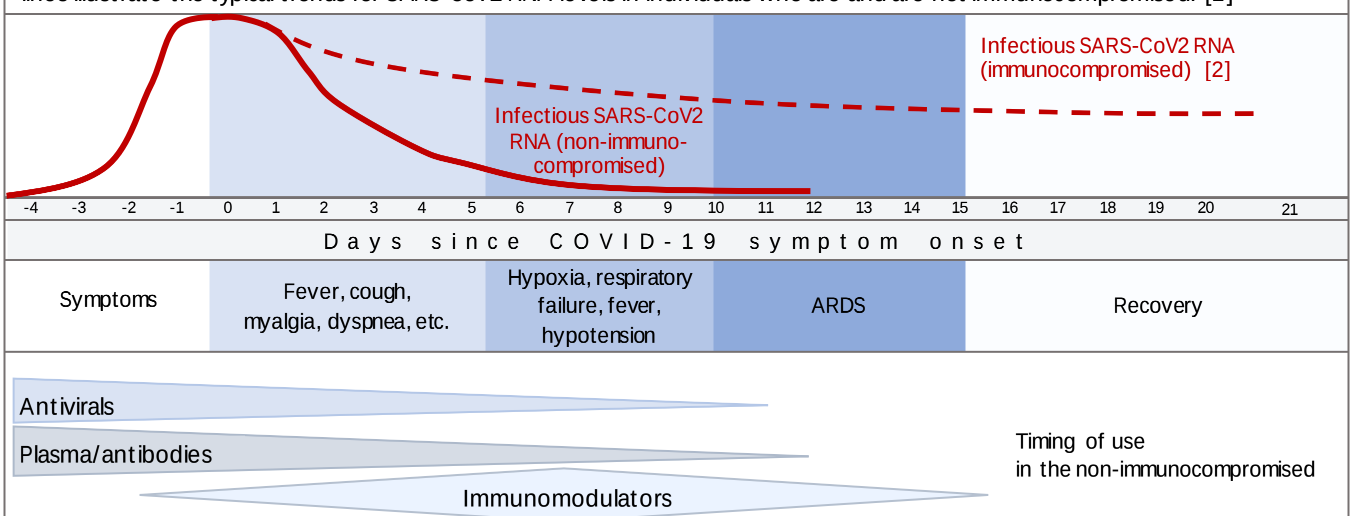
Vascular disease: Microvascular thrombosis and venous thromboembolism also occur with severe COVID-19.[28-30]

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 a 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)

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 [mAbs] 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]

Hospitalized patients: 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 oxygen saturation (SaO2) <94%, to receive 10 days of RDV or placebo. RDV was stopped for participants 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 with 15 days among those in the placebo arm (P<.001).[36] Results suggested a trend, although 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 participants 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. On day 14, 60% of participants in the 5-day arm were discharged from the hospital compared with 52% in the 10-day arm, and 8% of the 5-day arm participants compared with 17% of the 10-day arm participants were receiving mechanical ventilation or ECMO. By day 14, 8% of participants in the 5-day arm had died compared with 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 with the standard of care group.[38]

The SOLIDARITY study was 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 the 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 with standard of care (risk ratio [RR] 0.95; P=.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.

The DisCoVeRy Trial was an open-label, 4-arm RCT that included standard of care and RDV arms and enrolled 857 hospitalized adults requiring supplemental oxygen, with any duration of time since symptom onset.[40] There were 429 participants in the RDV arm and 428 in the standard of care arm; 70% of participants were men, 59% received oxygen via nasal canula or face mask, and 18% received invasive mechanical ventilation. World Health Organization, ordinal scale scores, were used to compare outcomes in the 2 arms at day 15 (primary endpoint) and day 28 (secondary endpoint), with no difference found based on either endpoint or stratification by disease severity at enrollment. The median decrease in viral RNA on nasal swabs was similar in the 2 arms. The decreased effect of RDV in this study, compared with the results of the ACTT-1 study, may be due to the longer time to initiation of RDV after symptom onset in this study.

The findings of no benefit with RDV in both the SOLIDARITY and DisCoVeRy RCTs suggest that the benefit of RDV may be small and may be limited to a subset of people hospitalized with COVID-19.

A retrospective study from the Veterans Health Administration hospital system used 2 methods to reduce confounding—propensity score matching and marginal structural models with inverse probability weighting—to compare 30-day mortality and time to discharge among individuals treated with RDV and matched control individuals.[41] In the adjusted analyses, there was no statistical difference in mortality (12% among those receiving RDV vs. 10% among those who did not). Time to discharge was longer among those who received RDV, but this was attributed to delaying discharge to complete a 5-day course of RDV.

Analysis of the experience at Johns Hopkins Medical Institutions (JHMI) suggests improved outcomes among participants who received RDV compared with matched participants who did not.[42]

On October 22, 2020, the U.S. Food and Drug Administration (FDA) approved RDV for the treatment of adult and pediatric patients ≥12 years old who require inpatient care for treatment of COVID-19.

Ambulatory patients: The PINETREE study compared 3 days of outpatient RDV infusion (200 mg day 1 and 100 mg on days 2 and 3) to placebo among unvaccinated ambulatory patients ≥12 years old who had ≥1 risk factor for severe COVID-19 and ≤7 days of symptoms.[43] Characteristics among the 279 RDV and 283 placebo patients were balanced with a mean age of 50, 50% women, and 61% with diabetes mellitus as the primary risk for severe COVID-19. The primary outcome was COVID-19-related hospitalization or death 28 days after enrollment. In the RDV arm, 2 (0.7%) participants had a COVID-19-related hospitalization compared to 15 (5.3%) in the placebo arm (p=0.008), for a relative risk reduction of 87%. There were no deaths in either arm. Adverse events were similar in both arms.

Access to RDV in JHMI ambulatory settings: RDV is not currently available for outpatient administration in the JHMI system. When available, to maximize potential benefit, RDV should be administered within 7 days of symptom onset. Access will be limited, and subgroups may be prioritized within patients who:

- ≥12 years old and weight ≥40 kg
- Have mild to moderate symptomatic COVID-19 disease, with ≤7 days of symptoms
- Are at high risk for severe COVID-19 disease (i.e., meet at least 1 of the following criteria):
    - BMI ≥25 kg/m^2
    - CKD (eGFR <60 mL/min/mm^3)
    - Diabetes
    - Pregnancy
    - Immunosuppressive disease with ongoing immune deficiency
    - Currently receiving immunosuppressive treatment
    - Cardiovascular disease or hypertension
    - Chronic lung disease (e.g., chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis, pulmonary hypertension)
    - Sickle cell disease
    - Neurodevelopmental disorders (e.g., cerebral palsy) or conditions conferring medical complexity, including severe congenital abnormalities, genetic or metabolic syndromes
    - Medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive-pressure ventilation requirement not related to COVID-19)

Who is likely to benefit from RDV treatment? For hospitalized patients, the ACTT-1 study reported no significant difference in RDV effect among study participants with ≤10 or >10 days of COVID-19 symptoms. An RCT from China reported a trend toward improved outcomes among participants with a shorter duration of symptoms (<10 days).[44] In the study, which compared 5 versus 10 days of RDV treatment, 62% of participants with <10 days of symptoms at the time of first RDV dose were discharged from the hospital compared with 49% of those with ≥10 days of symptoms.[44] 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, 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 [CI], 0.64–1.42). The subgroup analysis found the greatest 14-day mortality difference in the group requiring supplemental oxygen via nasal cannula (95% CI) based on oxygen requirement at enrollment.

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.

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.[31,32,45-48] This effect is analogous to other acute viral infections (e.g., influenza, norovirus, respiratory syncytial virus) in patients with substantial immunodeficiency.[49,50] Treatment with antiviral medications, such as RDV, may change the course of COVID-19 disease in patients with persistent SARS-CoV-2 replication. Several case reports have suggested this, some using multiple 10-day courses of RDV,[45,46] in which use of RDV 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.[45,51,52] Integrating Ct values into the clinical assessment may offer supportive evidence of ongoing SARS-CoV-2 replication causing disease (e.g., Ct ≤30 cycles).[45,52] 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.[45,46] 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 mAb therapies for patients previously treated with these agents. Notably, monoclonal anti–SARS-CoV-2 spike protein antibodies are authorized for use only in a nonhospital setting; an Emergency Investigational New Drug (EIND) application is currently required for use in hospitalized patients (see information below for accessing the product through this mechanism).

Adverse events: Adverse events from RDV or COVID-19 reported in clinical trials[37,53] include acute respiratory failure, anemia, gastrointestinal symptoms (constipation, nausea, vomiting, diarrhea), hypoalbuminemia, hypokalemia, increased bilirubin, infusion-related reactions (hypotension, nausea, vomiting, diaphoresis, shivering), and thrombocytopenia. Rare or occasional adverse effects reported in clinical trials[37,53] include hypoglycemia, insomnia, elevated prothrombin time (without a change in international normalized ratio), pyrexia, rash, and elevated transaminase level.

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.[36,44] 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 serious adverse events (SAEs) than the 5-day arm (35% vs. 21% of participants), 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 treatment course completion: 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 cytochrome P450 (CYP)2C8, CYP2D6, CYP3A4, and organic anion transporting polypeptide (OATP)1B1 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.[54] 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 estimated glomerular filtration rate (eGFR) <30 mL/min/m^2 or receiving renal replacement therapy. Concerns regarding 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 Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Veklury (remdesivir)].

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 end-stage renal disease on dialysis or a range of chronic kidney disease (CKD) stages who received RDV did not identify any increased risk of adverse effects or further renal impairment.[55] In addition, intravenous 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.[56-62]

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 upper limit of normal (ULN) or the patient develops symptoms of drug-induced liver injury, RDV should be discontinued and should not be restarted during the hospital admission.

Creatinine daily: Clinicians should discontinue RDV if there is a decline ≥50% in eGFR while evaluating for causes of acute kidney injury.

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

Table 3: JHHS Formulary Management and Medication-Use Policy Committee Restriction for Remdesivir for Hospitalized Patients Diagnosed with COVID-19 [a]

Use requested outside of the criteria below requires approval by the JHHS COVID-19 Drug Approval group.

Population	Criteria for Authorized Use	Treatment Duration and Comments
Immunocompetent patients	• ≤10 days symptoms • Respiratory compromise at time of clinical evaluation: SaO_2 ≤94% on room air for ≥1 hour *or* supplemental O_2 required to maintain SaO_2 >94% for ≥1 hour *or* documented sustained respiratory rate ≥24 breaths per minute • Mechanical ventilation or ECMO not allowed unless within ≤24 hours.	• **Treatment duration:** 5 days [b,c] • **Patients with impaired liver function:** If ALT increases to >10 times the ULN or the patient develops other signs or symptoms of hepatotoxicity, RDV must be discontinued. • **Patients with impaired kidney function:** If eGFR <30 mL/min, medical record documentation of risk vs. benefits discussion with the patient and patient consent to RDV treatment is required. [d]
Substantially immunodeficient patients [e]	• ≤21 days symptoms or first SARS-CoV-2 PCR (current COVID-19–related symptoms are not necessary) *or* • If >21 days symptoms or first SARS-CoV-2 PCR, SARS-CoV-2 RT-PCR with cycle threshold ≤30 cycles**.** If cycle threshold testing is not available onsite, other evidence of ongoing viral infection is required.	• **Treatment duration:** 5 days [b,c] • **Request for 5 additional days:** ID attending or consultant can approve requests for 5 additional days of RDV (sequential or subsequent to prior courses) [f]; rationale for approval must be documented in the patient's medical record. [g] • **Concomitant baricitinib treatment:** Patients can receive 10-day course of RDV. • **Patients with impaired liver function:** If ALT increases to >10 times the ULN or the patient develops other signs or symptoms of hepatotoxicity, RDV must be discontinued. • **Patients with impaired kidney function:** If eGFR <30 mL/min, medical record documentation of risk vs. benefits discussion with patient and patient consent to RDV treatment is required. [d]
Immunocompetent patients, not requiring O_2 and hospitalized for reasons other than COVID-19 (e.g., incidentally diagnosed on screening or nosocomial, AND not previously treated with sotrovimab)	• Must have new (within past 7 days) symptoms of mild to moderate COVID-19, not otherwise attributable, and not the primary reason for the patient's hospitalization: fever, chills, dyspnea, cough, pharyngitis, myalgia, diarrhea, emesis, dysgeusia, or anosmia. • No supplemental O_2 requirement allowed • Expected hospitalization of ≥3 days	• **Treatment duration:** 3 days • **With a new supplemental O_2 requirement,** patients may qualify for a 5-day course of RDV, which must be approved as determined by each hospital in the JHMI system. [h] • **Patients with impaired liver function:** If ALT increases to >10 times the ULN or the patient develops other signs or symptoms of

Table 3: JHHS Formulary Management and Medication-Use Policy Committee Restriction for Remdesivir for Hospitalized Patients Diagnosed with COVID-19 [a] *Use requested outside of the criteria below requires approval by the JHHS COVID-19 Drug Approval group.*		
Population	**Criteria for Authorized Use**	**Treatment Duration and Comments**
	• Meet EUA criteria for sotrovimab but unable to access sotrovimab due to unavailable supply or JHMI Monoclonal Antibody Prioritization Plan	hepatotoxicity, RDV must be discontinued. • **Patients with impaired kidney function:** If eGFR <30 mL/min, medical record documentation of risk vs. benefits discussion with patient and patient consent to RDV treatment is required. [d] • Patients are not to be admitted solely for RDV infusion.

Abbreviations: ALT, alanine transaminase; CYP3A4, cytochrome P450; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; JHMI, Johns Hopkins Medical Institutions; O_2, oxygen; PCR, polymerase chain reaction; SaO_2, oxygen saturation; RDV, remdesivir; RT-RCR, reverse transcriptase polymerase chain reaction; ULN, upper limit of normal

Notes:

a. *Transfers:* Patients transferred to JHHS from an outside hospital on RDV can complete their 5-day course of therapy (without JHHS Formulary COVID-19 Committee review).

b. *Discharges:* Completion of RDV course is not required for patients well enough for discharge.

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

d. *Patients with impaired renal dysfunction:* This Writing Group does not view renal dysfunction as a contraindication to RDV therapy because 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.

e. *Patients with substantial immunodeficiency:* Includes patients with solid organ or bone marrow transplant/hematopoietic stem cell transplant; hematologic malignancy, such as leukemia, lymphoma, myeloma, or severe B-cell depletion (e.g., common variable immune deficiency [CVID]); receiving rituximab or other anti-CD20-based treatment).

f. *Additional 5 days of RDV required approval:* **JHH:** Must be approved by an ID attending physician currently on hospital inpatient service (i.e., Mann, Solo Mann, Transplant Teaching, Transplant Solo, Polk, Tucker); **JHBMC, HCGH, SMH, JHACH:** Must be approved by an ID Consultant; **SH:** Must be approved by the SH Remdesivir Team

g. *Documentation:* The note should include signs and symptoms suggestive of ongoing viral replication and lack of alternative explanations. Assessment and documentation of a PCR-cycle threshold are not mandatory but may be additionally supportive.

h. *Approval for RDV use with ≥10 days of symptoms:* **JHH:** Must be approved by an ID attending physician currently on hospital inpatient service (i.e., Mann, Solo Mann, Transplant Teaching, Transplant Solo, Polk, Tucker); **JHBMC, HCGH, SH, SMH, JHACH:** Must be approved by an ID Consultant.

1/13/2022

☐ Nirmatrelvir/Ritonavir (Paxlovid)

Nirmatrelvir is a SARS-CoV-2 3CLpro protease inhibitor dosed as nirmatrelvir 300 mg plus ritonavir 100 mg twice daily for 5 days. The EPIC-HR RCT enrolled unvaccinated outpatient adults (≥18 years old) at risk for progression to severe COVID-19 and ≤5 days of symptoms at the time of randomization. The primary endpoint was hospitalization or death 28 days from randomization. In the interim analysis of results in 2,085 participants, 8 (0.8%) in the nirmatrelvir arm reached the primary endpoint compared to 66 (6.3%) in the placebo arm (relative risk reduction 88%, p=0.001). No deaths occurred in the nirmatrelvir arm compared to 12 in the placebo arm. Adverse events were overall lower in the nirmatrelvir arm.

Based on EPIC-HR results, the FDA issued an EUA for Paxlovid on December 22, 2021, for COVID-19 outpatients or inpatients admitted for non-COVID-19 reasons with ≤5 days of COVID-19 symptoms *and* mild or moderate COVID-19 *and* risk factors for severe COVID-19 disease. For more information, see FDA > Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19.

Ritonavir is a potent inhibitor of cytochrome P450 3A4; evaluate for drug-drug interactions before administering this medication. Consult with a clinical pharmacist to assist with preemptive dose adjustments for patients receiving concomitant therapy with tacrolimus, cyclosporine, sirolimus, or everolimus. Consider consultation with a clinical pharmacist for other drug-drug interactions between ritonavir and current patient medications.

Eligibility criteria: Ambulatory patients who meet the following criteria are eligible for Paxlovid treatment:

- Aged ≥12 years old, with weight ≥40 kg
- Mild to moderate COVID-19, without need for supplemental oxygen due to COVID-19 disease
- At high risk for progression to severe COVID-19, hospitalization, or death (CDC criteria):
  - BMI ≥30 kg/m2
  - CKD (eGFR <60 mL/min/mm^3)
  - Diabetes mellitus
  - Pregnancy or recent pregnancy
  - Immunosuppressive disease with ongoing immune deficiency
  - Currently receiving immunosuppressive treatment
  - Cardiovascular disease or hypertension
  - Cerebrovascular disease
  - Chronic lung disease (e.g., chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis, pulmonary hypertension)
  - Sickle cell disease
  - Neurodevelopmental disorders (e.g., cerebral palsy) or conditions conferring medical complexity, including severe congenital abnormalities, genetic or metabolic syndromes
  - Medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive-pressure ventilation requirement not related to COVID-19)

Prioritization: The Maryland State Department of Health recommends prioritizing patients who meet the NIH criteria for being at highest risk for severe disease. See NIH > COVID-19 Treatment Guidelines > The COVID-19 Treatment Guidelines Panel's Interim Statement on Patient Prioritization for Outpatient Anti-SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints.

Administration: Paxlovid (nirmatrelvir 300 mg/ritonavir 100 mg) is taken by mouth twice daily for 5 days. It is administered as 3 tablets taken together: 2 tablets of nirmatrelvir 150 mg plus 1 tablet of ritonavir 100 mg.

- Patients with moderate renal impairment (eGFR ≥30 to <60 ml/min.): Reduce nirmatrelvir dose to 150 mg plus 100 mg ritonavir by mouth twice daily for 5 days.
- Patients with severe renal impairment (eGFR <30 mL/min.): Paxlovid is not recommended.
- Patients with severe hepatic impairment (Child-Pugh Class C): Paxlovid is not recommended.

Drug-drug interactions: Ritonavir is a potent inhibitor of cytochrome P450 3A4; evaluate for drug-drug interactions before, during, and for up to 2 weeks after administration of this medication. Consult with a clinical pharmacist to assist with preemptive dose adjustments for patients receiving concomitant therapy with tacrolimus, cyclosporine, sirolimus, or everolimus. Consider consulting with a clinical pharmacist regarding any other potential drug-drug interactions between ritonavir and a patient's current medications.

Access: Licensed prescribers can submit a prescription to a pharmacy that has the medication in stock; see the Maryland State Medical Society (MedChi) Coronavirus Resource Center for a list of pharmacies that have this medication in stock. Prescribers must inform patients that Molnupiravir is available through an FDA EUA and is not yet FDA-approved.

☐ Molnupiravir

Molnupiravir is a ribonucleoside prodrug with activity against SARS-CoV-2 and other RNA viruses. In the MOVe-OUT trial, at-risk, non-hospitalized adults (≥18 years old) with ≤5 days of symptoms were randomized to receive either molnupiravir 800 mg twice daily or placebo, each for 5 days.[63] The primary endpoint was any-cause hospitalization or death through day 29. Obesity was the most common risk factor (74%) among the 1,433 participants. In the modified intention-to-treat analysis, 48 (6.8%) of the molnupiravir arm participants compared to 68 (9.7%) of placebo arm participants were hospitalized or died (RR 31%; CI 0.48-1.01). Adverse events were similar in both arms.

Based on the MOVe-OUT trial results, the FDA issued an EUA for molnupiravir on December 23, 2021, for outpatient treatment of mild to moderate COVID-19 in patients at high risk of progression to severe COVID-19. For more information, see FDA > Frequently Asked Questions on the Emergency Use Authorization for Molnupiravir for Treatment of COVID-19

Eligibility criteria: Ambulatory patients who meet the following criteria are eligible for Molnupiravir treatment when Paxlovid or monoclonal antibodies are not available:

- Aged ≥18 years old, with weight ≥40 kg
- Mild to moderate COVID-19, without need for supplemental oxygen due to COVID-19 disease
- At high risk for progression to severe COVID-19, hospitalization, or death (CDC criteria):
  - BMI ≥30 kg/m2
  - CKD (eGFR <60 mL/min/mm^3)
  - Diabetes mellitus
  - Pregnancy or recent pregnancy
  - Immunosuppressive disease with ongoing immune deficiency
  - Currently receiving immunosuppressive treatment
  - Cardiovascular disease or hypertension
  - Cerebrovascular disease
  - Chronic lung disease (e.g., chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis, pulmonary hypertension)
  - Sickle cell disease
  - Neurodevelopmental disorders (e.g., cerebral palsy) or conditions conferring medical complexity, including severe congenital abnormalities, genetic or metabolic syndromes
  - Medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive-pressure ventilation requirement not related to COVID-19)

Prioritization: The Maryland State Department of Health recommends prioritizing patients who meet the NIH criteria for being at the highest risk for severe disease. See NIH > COVID-19 Treatment Guidelines > The COVID-19 Treatment Guidelines Panel's Interim Statement on Patient Prioritization for Outpatient Anti-SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints.

Administration: Molnupiravir 800 mg is taken by mouth every 12 hours for 5 days (four 200 mg capsules). No dose adjustment is required for patients who have kidney or liver disease.

Access: Licensed prescribers can submit a prescription to a pharmacy that has the medication in stock; see the Maryland State Medical Society (MedChi) Coronavirus Resource Center for a list of pharmacies that have this medication in stock. Prescribers must inform patients that Molnupiravir is available through an FDA EUA and is not yet FDA-approved.

☐ 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 (PEP) and treatment for hepatitis A and B, mumps, polio, measles, rabies, SARS-CoV-1, MERS-CoV, and Ebola.[64-68] 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.[68] 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.[69] The primary outcome, clinical improvement within 28 days, was similar in the 2 arms.
- An RCT from the Netherlands was halted early for futility.[70] 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 multinational open-label RCT (CONCOR-1) using mixed plasma titers with 940 participants hospitalized with ≤12 days of respiratory symptoms reported no difference in the combined primary endpoint of mortality or intubation (32% for convalescent plasma and 28% for standard of care; *P*=.18).[71] Receipt of lower-titer convalescent plasma was associated with higher odds of the primary endpoint. The median duration of symptoms at enrollment was 8 days, and 18% of participants were in the intensive care unit (ICU) when enrolled.
- An open-label RCT from Spain used a mix of plasma titers in 350 hospitalized participants who had ≤7 days of symptoms and were receiving mechanical ventilation or high-flow oxygen. The study reported no difference in the primary outcome of progression to high-flow oxygen, ventilation, ECMO, or death at 14 days (11.7% in the convalescent plasma and 16.4% in the standard of care arms; *P*=.2). The study did find a difference at 28 days favoring convalescent plasma (8.4% vs. 17%; *P*=.021).[72] No association between outcome and antibody titer was found.
- 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.[73] 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 or placebo.[74] At day 15, more participants in the placebo arm (31%) than in the convalescent plasma arm (16%) developed severe respiratory disease (*P*=.02).
- A placebo-controlled RCT from the United States randomized 511 participants from an emergency department (ED) who were ≥50 years old, had a risk factor for severe COVID-19, had ≤7 days of symptoms, and were likely to be discharged home from the ED.[75] The primary endpoint was a composite of repeat ED visits, hospitalization, or death 15 days from randomization. The trial was halted early for futility. In the convalescent plasma arm, 30% reached the primary endpoint compared with 31.9% in the placebo arm. There was also no difference in 30-day mortality.
- A component of the international open-label REMAP-CAP study compared outcomes in groups treated with high titer convalescent plasma vs. standard of care. In this report, results for critically ill participants (this report) included those of 1,084 who received convalescent plasma and 916 who received standard of care.[76] The primary outcome was the number of organ support–free days up to day 21, with 28-day survival as a

secondary outcome. There was no difference between arms based on the primary outcome, secondary outcomes, or subgroup analysis.

The results of these RCTs suggest that early use of higher-titer 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 FDA expanded access program (EAP) indicated overall relative safety (though not compared with 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.[77] Lower mortality (7-day and 30-day) was reported in those who received convalescent plasma ≤3 days from COVID-19 diagnosis 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, or high SARS-CoV-2 spike subunit antibody titers (measured after transfusion). Among participants who received a high-titer unit (SARS-CoV-2 immunoglobulin [Ig]G signal-to-cutoff [S/Co] ratio ≥18.45), 30-day mortality was 16% compared with 25% in those who received a low-titer unit (SARS-CoV-2 IgG S/Co ratio ≤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.[77] 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.

In a secondary analysis of this population, participants receiving plasma sourced within 150 miles had a lower risk of mortality than those receiving plasma sourced >150 miles from the home address (8.6% compared with 10.8%; *P*<.001).[78]

A large retrospective study from HCA Healthcare that included 4,337 participants who received convalescent plasma and 8,708 who did not report lower mortality in those who received convalescent plasma (hazard ratio, 0.71; *P*<.001). A difference in mortality was observed for those who received convalescent plasma within 3 days of hospital admission but not among those who received it 4 to 7 days after admission.[79]

Novel variants (including Omicron) and convalescent plasma: It is unclear whether novel variants will diminish any potential *in vivo* benefit of convalescent plasma. An *in vitro* study of convalescent plasma from donors without vaccination, with an initial vaccination series, with vaccination after SARS-CoV-2 infection, and with boosted mRNA vaccination. The authors reported loss of neutralizing activity in convalescent plasma from donors who had received the initial vaccine series only and good neutralizing activity in convalescent plasma from donors vaccinated after a primary SARS-CoV-2 infection and donors who had received an mRNA booster dose 6 months after the primary series.[80] Another *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.[81]

The clinical implications of convalescent plasma use in patients with the Omicron or other variants of concern are not clear. In addition, widely used neutralization assays are based on earlier strains of SARS-CoV-2 and do not reflect neutralization of Omicron or other newer variants.

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 1 study that found a statistically significant benefit[74]) and, possibly, before hospitalization (although the FDA EUA does not currently allow administration of convalescent plasma in ambulatory patients).

The risks associated with the use of convalescent plasma include a very low risk of pathogen transmission (~1 in 2 million units),[68,82,83] allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.[82,83] A review of convalescent plasma therapy for severe or life-threatening COVID-19 in 5,000 participants in the United States found that SAEs at 4 hours post-administration occurred in <1%.[84] An updated analysis of safety among 21,987 participants who received convalescent plasma in the United States as part of the FDA EAP reported low rates of SAEs,[85] most of which were judged not to be related to the plasma. Venous thromboembolic disease was reported in <1% of participants, cardiac events in 3%, and transfusion events in <1%, including cases of TRALI in 0.18% and cases of TACO in 0.10%. These analyses provide evidence for the safety but 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: On December 28, 2021, the FDA updated the EUA to authorize convalescent plasma use (high titer only) **only for patients who are immunosuppressed or receiving immunosuppressive therapy, whether hospitalized or ambulatory.** Acquisition of appropriate high-titer convalescent plasma units will take time; when it is available, it's likely the supply will be limited.

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 6 available kits. See December 28, 2021, EUA Appendix A.
- Administration should be initiated with 1 unit (200 mL). Additional convalescent plasma units may be administered based on a patient's clinical response.
- Physicians should consider using 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 a consent form 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 after infusion to have the blood bank send an aliquot to the JHMI Immunology Lab. The lab will use the FDA-approved EUROIMMUN assay to measure the plasma titer. If the unit is low titer, the clinician can consider administering a second unit. Second units are not routinely administered if the first unit is high titer.
- Clinicians may contact the blood bank or their institution at JHUcovidplasma@jhmi.edu. See the information above regarding the procurement of high-titer units at JHH.

Considerations for Use: 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 old), and are immunosuppressed or receiving immunosuppressive therapy. Available clinical trial data demonstrated benefit when high-titer convalescent plasma was administered within 3 days of symptom onset in elderly patients with mild or moderate COVID-19.[57] A specific duration of symptoms is no longer specified because an individual with humoral immunity may fail to develop neutralizing antibodies even over an extended period. Administration of subsequent units should be considered based on clinical response

B. Antibody Mediation or Neutralization

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

Omicron Variant Neutralization: Neither casirivimab/imdevimab nor bamlanivimab/etesevimab display *in vitro* effectiveness against the Omicron variant of SARS-CoV-2 (see CDC Science Brief: Omicron (B.1.1.529) Variant and Regeneron Omicron Statement November 30, 2021). Sotrovimab is the only mAb recommended for use in patients with known or suspected Omicron variant infection.

☐ Monoclonal and Polyclonal Neutralizing Antibodies

Although their mechanism of action is much the same as that hypothesized for convalescent plasma, mAbs or polyclonal antibodies (pAbs) are synthetic antibodies directed toward the SARS-CoV-2 spike protein. Bamlanivimab/etesevimab has reduced activity against the Beta variant but not the Delta variant. Casirivimab/imdevimab has *in vitro* activity against some variants to which bamlanivimab/etesevimab has reduced activity.

Bamlanivimab (LY-CoV555), bamlanivimab/etesevimab: The studies discussed below were conducted before the emergence of the SARS-CoV-2 Omicron variant.

Preliminary A phase 2 clinical trial conducted before the emergence of variants of concern randomized 452 outpatients to receive a low, medium, or high dose of the mAbs or placebo, with a change in SARS-CoV-2 RNA at day 11 compared with baseline as the primary endpoint.[86] Participants had confirmed COVID-19 and at least 1 COVID-19–related symptom but no need for supplemental oxygen. A significant reduction in ED visits and (predominantly) hospitalization was observed in the pooled mAbs arms (1.6%) compared with the placebo arm (6.3%); the most significant difference was observed in the subgroup analysis with participants aged ≥65 years or with a body mass index (BMI) ≥35kg/m^2 (4% in the mAbs arms and 15% in the placebo arm). 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 SAEs in either group.

The BLAZE-1 placebo-controlled RCT randomized 1,035 ambulatory participants to receive bamlanivimab/etesevimab (n=518) or placebo (n=517), with a primary outcome of death or COVID-19–related hospitalization.[87] In the placebo arm, 36 (7%) participants were hospitalized, and 10 died, compared with 11 (2.1%) hospitalizations and no deaths in the treatment arm, a statistically significant result.

Because bamlanivimab/etesevimab was effective against the SARS-CoV-2 Delta variant, which accounted for 99% of viral isolates sequenced in the United States in summer 2021, the FDA resumed the release of these mAbs. (The FDA had temporarily paused the distribution of bamlanivimab/etesevimab due to reduced susceptibility of the Beta (B.1.351) and Gamma (P.1) SARS-CoV-2 variants of concern.

Casirivimab/imdevimab (REGEN-COV): The studies discussed below were conducted before the emergence of the SARS-CoV-2 Omicron variant.

The preliminary analysis included 275 outpatients with COVID-19 confirmed by nucleic acid amplification test who were enrolled and randomized 1:1:1 to receive a low or high dose of casirivimab/imdevimab or placebo.[88] Before receiving the casirivimab/imdevimab, 45% of patients were seropositive, and 41% were seronegative; serostatus was not determined for 14% of participants. casirivimab/imdevimab reduced SARS-CoV-2 PCR levels in samples from the nasopharynx through day 7. The reduction was most notable for participants who were seronegative at enrollment and had the highest viral loads. A 95% reduction in viral load was found in this group compared with the placebo group. Symptom resolution occurred in 13 days in the placebo group, 8 days in the high-dose group (P=.22), and 6 days in the low-dose group (P=.09).

These findings led the FDA to issue an EUA on November 21, 2020. The FDA updated the 9/16/2021 EUA to authorize the following:

- Dose reduction to casirivimab 600 mg/imdevimab 600 mg.

- Subcutaneous administration when the intravenous infusion is not feasible or would delay treatment.
- Use of a coformulated, single-vial product.

A casirivimab/imdevimab 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 casirivimab/imdevimab arm of the RECOVERY trial, 9,785 hospitalized participants were randomized to receive either casirivimab 4,000 mg/imdevimab 4,000 mg 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 casirivimab/imdevimab (24%) than in the group that received care as usual (30%).[89] Similar findings were reported from a study of hospitalized participants receiving either low-flow or no supplemental oxygen at enrollment.[90] Most outcomes trended toward superiority for casirivimab/imdevimab, with the secondary outcome of death or mechanical ventilation lower among participants seronegative for anti–SARS-CoV-2 spike at baseline: 10.3% and 19.4% in the casirivimab/imdevimab and placebo arms, respectively.

Sotrovimab: Interim analysis of results from an RCT of 583 nonhospitalized adults with mild COVID-19 symptoms for ≤5 days found an 85% reduction in the risk of hospitalization or death with sotrovimab compared with placebo.[91] 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. **Only sotrovimab has relevant neutralizing activity against Omicron.**

Dosing and administration: Sotrovimab is administered as a one-time, 500 mg intravenous infusion over at least 60 minutes. Infusion must be performed in a staffed setting that is equipped to monitor patients for 1 hour post-infusion and manage severe infusion reactions, such as anaphylaxis. See FDA > Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Sotrovimab.

Access to mAbs for outpatient* administration (sotrovimab, casirivimab/imdevimab, and bamlanivimab/etesevimab): Casirivimab/imdevimab and bamlanivimab/etesevimab have no relevant activity against the Omicron variant and should not be used while Omicron accounts for >80% of SARS-CoV-2 variants. They can be obtained only if genomic sequencing demonstrates that the infecting SARS-CoV-2 is not the Omicron variant.

These mAbs should be administered early in infection (or within 7 days of symptom onset) to maximize any potential benefit (i.e., as for PEP). Access is limited to:

- Clinical trials
- FDA EUAs for ambulatory patients
- At JHH, an EIND application for specific high-risk patients with symptomatic COVID-19 (see Appendix B: Johns Hopkins Medicine Umbrella Protocol for Requests for Emergency Use of Casirivimab/Imdevimab and Remdesivir
- Per the EUA, patients who are ≥65 years old or 12 to 17 years old with weight ≥40 kg[92]; have mild symptomatic COVID-19 disease, ≤10 days of symptoms, and no supplemental oxygen requirement; are at high risk of developing severe COVID-19 disease (meets at least 1 of the following criteria):
    - BMI ≥25 kg/m^2
    - CKD (eGFR <60 mL/min/mm^3)
    - Diabetes
    - Pregnancy
    - Immunosuppressive disease with ongoing immune deficiency
    - Currently receiving immunosuppressive treatment
    - Cardiovascular disease or hypertension
    - Chronic lung disease (e.g., chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis, pulmonary hypertension)
    - Sickle cell disease

- Neurodevelopmental disorders (e.g., cerebral palsy) or conditions conferring medical complexity, including severe congenital abnormalities, genetic or metabolic syndromes
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive-pressure ventilation requirement not related to COVID-19)

*** Note:** In-hospital use for high-risk patients admitted for a non–COVID-19 indication who have mild (no supplemental O2) COVID-19.

Current local availability: See Maryland Referral Form: Ambulatory Monoclonal Antibody Infusion Treatment for COVID-19 for referral information and locations (listed on page 3). Additional venues may be available in certain EDs, Johns Hopkins Weinberg Infusion Center (available only for cancer patients), Park Building Infusion Suite, Johns Hopkins Homecare/Pharmaquip, 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.

Note: Only sotrovimab is effective against the Omicron variant. Supplies are limited, and infusion centers are prioritizing referrals based on product availability.

☐ 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.[93,94] 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 participants with <7 days of symptoms and RBV plus LPV/RTV with LPV/RTV alone in participants with 7 to 14 days of symptoms.[95] Participants with <7 days of symptoms who received IFN beta-1b had a shorter time to RT-PCR results for SARS-CoV-2 and symptom resolution.[95] IFN beta-1b likely provided most of the clinical benefit observed in this study; however, a placebo-controlled phase 3 trial would help confirm findings.

C. Immune Modulation

Box 3: 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 to treat COVID-19 only in 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 intravenously 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.

☑ **Tocilizumab and baricitinib [a,b]:** Tocilizumab 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 with evidence of clinical progression of COVID-19 are most likely to benefit.

- Note that tocilizumab may be preferred over baricitinib in ICU and pregnant patients based on limited data regarding the use of baricitinib in these populations.
- Subgroup analysis of the REMAP-CAP trial reported response to tocilizumab across all terciles of CRP levels at study entry. In the RECOVERY trial, CRP was included in the entry criteria. Measurement of IL-6 levels was not part of entry criteria or subgroup analysis in EMPACTA, REMAP-CAP, and

Box 3: Recommendations for the Use of Immune Modulatory Agents to Treat COVID-19

RECOVERY. Neither CRP nor IL-6 values should be used in assessing patients with progressive SARS-CoV-2 infection for tocilizumab treatment.

- Tocilizumab and baricitinib can be used only with the approval of the JHHS Formulary COVID Drug Approval Committee. The Committee membership includes Brent Petty (JHH), Amy Knight (JHBMC), Bruce Ludwig (HCGH), Amirali Nader (SH), and Mark Abbruzzese (SMH).
- The role of CRP values in determining potential response to tocilizumab is unclear. Therefore, if the JHHS Formulary COVID Drug Approval Committee denies tocilizumab treatment, the clinician may appeal the decision with the Vice President of Medical Affairs for the institution in which treatment was denied.
- When seeking approval for use, the clinician should ensure that the patient meets the EUA criteria for consideration: confirmed COVID-19, are hospitalized, are receiving systemic corticosteroids, and require supplemental oxygen (nasal canula, high-flow, mechanical ventilation, or ECMO).
- Discontinue if the patient is discharged before completing treatment.
- The decision to use baricitinib +/- RDV may benefit from discussion with an ID attending physician.
- **Tocilizumab dosing:**
  - <30 kg: 12 mg/kg intravenously over 60 minutes
  - ≥30kg: 8 mg/kg (max 800 mg) intravenously over 60 minutes
- **Baricitinib dosing:** 4 mg by mouth daily for a maximum of 14 days

☑ **Fluvoxamine:** Fluvoxamine may be considered for *outpatient* management of COVID-19 within 7 days of symptom onset when timely administration of monoclonal antibodies is not possible or is unlikely to occur.

- **Dosing:** Fluvoxamine 100 mg by mouth, twice per day for 10 days.

☑ **Others:** Use of the following agents as treatment for COVID-19 is recommended only in the setting of a clinical trial, in part because of uncertainties about combined immune suppression when used with dexamethasone or tocilizumab and the greater body of data supporting tocilizumab and baricitinib. Fewer data are available regarding agents from the same class as tocilizumab, such as sarilumab (also an IL-6 receptor antagonist), baricitinib, or other available immunomodulatory agents.

- Anti–GM-CSF mAb (e.g., lenzilumab)
- Anti–IL-1
- 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

For more information, see:

a. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Actemra (tocilizumab)
b. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Baricitinib

☐ Systemic Corticosteroids

The recommendation for the use of dexamethasone is based on findings from the RECOVERY trial[96] 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 prespecified 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.

Because the RECOVERY trial specifically used dexamethasone, the recommendations included in this guidance are for dexamethasone rather than any alternative corticosteroid, such as methylprednisolone.

RECOVERY trial: The RECOVERY trial, an 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.[96] The 2,104 participants randomized to the dexamethasone arm received 6 mg by mouth or intravenously 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 not receiving supplemental oxygen had a median of 6 days of symptoms. When their results were compared with those of 4,321 patients who received standard of care, the 28-day primary endpoint for mortality was 482 of 2,104 (22.9%) participants in the dexamethasone group and 1,110 of 4,321 (25.7%) participants in the placebo group (RR, 0.83; 95% CI 0.75–0.93). When subgroups were examined, mortality risk compared with standard of care was 0.65 (P=.0003) for participants on mechanical ventilation, 0.8 (P=.002) for those receiving noninvasive supplemental oxygen, and 1.22 (P=.1; a statistically nonsignificant increase in mortality) for those 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.

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 of an 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 nonpregnant patients. As noted above, prednisolone or hydrocortisone are reasonable alternatives for pregnant patients to achieve lower fetal glucocorticoid concentrations.

GLUCOCOVID trial: This 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.[97] 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, ICU admission, or 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.

Patients ≥70 years old: An observational study of ICU patients ≥70 years old with COVID-19 reported higher mortality among the 3,082 participants who received corticosteroids than among those who did not.[98] The association was maintained with adjustment for sequential organ failure assessment (SOFA) score and clinical frailty scale. Limitations of this study are that it did not use propensity matching or marginal structural models with inverse probability weighting, nor did it control for timing or dose of the corticosteroid.

Meta-analysis of systemic 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.[99] 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.[100]

☐ Inhaled Corticosteroids

The STOIC open-label RCT compared treatment with inhaled budesonide (400 µg doses of the dry turboinhaler powder twice per day) to standard of care among participants with ≤7 days of mild COVID-19 symptoms.[101] The primary endpoint was any COVID-19–related urgent or emergency care visit or hospitalization. In per-protocol analysis, 10 of 70 (14%) participants in the usual care group met the primary endpoint compared with 1 of 69 (1%) participants in the budesonide group (difference in proportions, 0.131; 95% CI, 0.043–0.218; *P*=.004). The intent-to-treat group had similar numbers, with 15% in the standard of care arm and 3% in the treatment arm meeting the primary endpoint. Symptom duration was 1 day less in the budesonide group.

The PRINCIPLE open-label, adaptive RCT compared inhaled budesonide (n=787) with standard of care (n= 1,069) in participants ≥65 years old or ≥50 years old with comorbidities who were not hospitalized and had ≤14 days of symptoms.[102] The composite primary endpoint was first self-reported recovery and hospital admission or death related to COVID-19 within 28 days. There was a benefit in time to first self-reported recovery of 2.94 days (95% Bayesian credible interval, 1·19 to 5·12) in the budesonide group compared with the standard of care group (11·8 days vs. 14·7 days).

☐ 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,[103] REMAP-CAP,[104] and RECOVERY[105] studies of tocilizumab, in which most of the participants received corticosteroids, 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 with placebo in the ACTT-2 study, primarily among participants receiving high-flow oxygen or noninvasive ventilation.[106] All participants received RDV; no data on corticosteroids were provided. The ACTT-4 study compared dexamethasone with 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.[107] Results of the LIVE-AIR study of the anti-GM-CSF mAb lenzilumab reported lower survival without ventilation failure for lenzilumab than placebo; most participants received corticosteroids and RDV.[108]

No studies are available comparing targeted immunomodulatory agents, nor are studies available assessing the use of multiple targeted immunomodulatory agents. Because of the 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.[109]

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[110] or clinical progression at 14 days[111]; 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 than among the group who received placebo (9% and 35%, respectively).[112]

In a press release (7/29/20), Roche announced that an RCT that included 450 participants with COVID-19 pneumonia and SpO_2<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 days vs. 28 days).[113,114]

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.[115] The hazard ratio of the primary outcome of progression to mechanical ventilation or death was 0.56 (P=.04) among those randomized to the tocilizumab arm compared with 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.[116,117]

The REMAP-CAP study, an international adaptive clinical trial platform for testing multiple COVID-19 therapeutics, examined tocilizumab or sarilumab compared with standard care.[118] Participants were adults with COVID-19 admitted to an ICU 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 was 10 days for tocilizumab and 0 days 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 a tocilizumab treatment arm.[105] Participants were first randomized to one of the following: usual care, dexamethasone, LPV/RTV, HCQ, 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% received high-flow oxygen or invasive or noninvasive mechanical ventilation, and 45% received supplemental oxygen via nasal cannula. The primary endpoint of 28-day mortality occurred among 29% of the tocilizumab group and 33% of the no-tocilizumab group (P=.007). In subgroup analysis, tocilizumab was most effective when used concomitantly with corticosteroids and 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.[119] 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% of those in the standard care arm. The study was halted early out of concern for potential harm to those remaining in the tocilizumab arm because mortality at day 15 occurred in 11 (17%) of tocilizumab recipients and 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.

Meta-analysis of IL-6R antagonist RCTs: A meta-analysis of 27 RCTs (placebo-controlled and open-label compared with usual care) included 9 published studies and 18 unpublished or preprint studies. Overall, there was lower mortality with tocilizumab treatment (OR, 0.86; P=.003).[120]

JAK inhibitors: JAK inhibitors such as baricitinib, ruxolitinib, and fedratinib are FDA-approved for treating rheumatoid arthritis, myelofibrosis, or polycythemia vera and lead to the downregulation of TNF-α, IL-5, IL-6, and IL-1B.[121] 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 with placebo and RDV, reported a statistically significant difference in the primary outcome of time to recovery. Participants in the baricitinib arm reached hospital discharge 1 day earlier than those in the placebo arm.[122] The ACTT-4 study compared the use of baricitinib with dexamethasone among individuals receiving RDV. After enrolling approximately 1,000 participants, the study was halted due to a low chance of identifying a difference between arms (see NIH closes enrollment in trial comparing COVID-19 treatment regimens).

With 21% of participants from the United States and most of the others from Latin American countries, the COV-BARRIER study randomized 1,526 participants with elevated inflammatory markers (CRP, lactate dehydrogenase, ferritin, or D-dimer) to receive baricitinib or placebo; 96% received corticosteroids, and 19% received RDV.[123] The primary outcome of progression to high-flow oxygen, noninvasive ventilation, invasive ventilation, ECMO, or death by day 28 was not significantly different between groups (27.8% for baricitinib vs. 30.5% for placebo; *P*=.2). All-cause mortality, a secondary outcome, was lower in the baricitinib group (8.1% for baricitinib vs. 13.1% for placebo; *P*=.002).

This writing group recommends tocilizumab as a first choice and baricitinib as an alternative agent if tocilizumab is not available based on the following:

- The greater number of tocilizumab RCTs than baricitinib RCTs.
- More clinical experience treating COVID-19 with tocilizumab than with baricitinib.
- Limited data on baricitinib use in patients being treated in ICUs.
- Results of animal studies that suggest possible teratogenicity for baricitinib.

GM-CSF inhibitors: Lenzilumab neutralizes human GM-CSF, which is a cytokine upstream from IL-6. *In vitro* data suggest it may limit CRS.[124] The LIVE-AIR study compared lenzilumab with placebo among 520 participants, of whom 93% received corticosteroids and 72% received RDV.[108] The primary outcome of survival without ventilation failure occurred among 15.6% of lenzilumab recipients and 22.1% of placebo recipients (*P*<.05); day 28 mortality occurred among 9.6% and 13.9% of lenzilumab and placebo recipients, respectively. The mortality benefit appeared greatest for those <85 years old 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 biological 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.[125] 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.[126]

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.[127] 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.[128] When used in an animal model of influenza, BTK inhibitors rescued mice from lethal lung injury.[129] 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.[130] A case series of 19 patients with COVID-19 treated with acalabrutinib suggested overall safety and reduced inflammatory markers.[131]

☐ Other Immune Modulators

Fluvoxamine: It has been hypothesized that this selective serotonin reuptake inhibitor may modulate the immune response through the sigma-1 receptor agonism.

A U.S.-based placebo-controlled outpatient RCT randomized adults with confirmed SARS-CoV-2 infection to receive 15 days of escalating doses of fluvoxamine (n=80) or placebo (n=72).[132] The primary endpoint was clinical deterioration. Clinical deterioration occurred in none of the participants in the fluvoxamine arm and 6 (8.3%) of those in the placebo arm. Pneumonia and gastrointestinal adverse events occurred more often in the placebo than in the treatment arm.

An outpatient study conducted in Brazil randomized high-risk participants to receive fluvoxamine 100 mg twice daily (n=739) or placebo (n=733) for 10 days.[133] At 28 days, ED visit (of greater than 6 hours duration) or hospitalization occurred in 77 (10.4%) participants in the fluvoxamine arm and 108 (14.7%) participants in the placebo arm, a statistically significant finding by Bayesian analysis.

☐ Intravenous Immune Globulin

IVIG (nonconvalescent) modulates immune response by interacting with antibodies and complementing and blocking immune cells' receptors.[134] IVIG has been used to treat multiple conditions, including SARS and COVID-19, to control pathogenic inflammation.[135] A case series of 3 patients reported using IVIG at the point of clinical deterioration and presumed shift to cytokine dysregulation.[136] 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. Treatment of COVID-19 in Pregnancy

Data are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes with the use of currently available COVID-19 therapeutics. None of the therapeutics commonly used to treat COVID-19 have been subject to dedicated testing in pregnancy; however, except for baricitinib, there are no known safety concerns. Agents should be considered during pregnancy only if the potential benefit outweighs the potential risk for the parent and the fetus. Treatment with specific agents should be discussed as part of shared decision-making among the patient, obstetrician, and consultants.

Monoclonal antibodies: Per the American College of Obstetricians and Gynecologists (ACOG), clinicians may consider the use of mAbs (e.g., casirivimab/imdevimab, sotrovimab) when indicated.

Nonclinical reproductive toxicity studies have not been conducted with casirivimab and imdevimab. No binding of clinical concern was detected in a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues. Human IgG1 antibodies are known to cross the placental barrier; therefore, mAbs have the potential to be transferred from the parent to the developing fetus. Whether the potential transfer of mAbs provides any treatment benefit or risk to the developing fetus is unknown.[137]

Remdesivir: Limited available information suggests that RDV does not pose a risk in pregnant individuals with COVID-19. In animal studies, RDV had no effect on embryo-fetal development.[138] In a clinical case series describing the compassionate use of RDV in 86 pregnant and postpartum patients, rates of adverse effects were low (as expected), and RDV was generally well tolerated.[139] A review surveying 12 case reports and published studies of RDV use in pregnant and lactating patients did not reveal serious safety signals.[140]

Paxlovid (nirmatrelvir plus ritonavir): Limited animal data suggest possible reduced fetal body weight. No other adverse fetal developmental outcomes were observed. There is no data from use in humans during pregnancy. See Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid.

Molnupiravir: The FDA fact sheet for the EUA states: "Based on animal data, molnupiravir may cause fetal harm." There are concerns for both teratogenicity and mutagenesis with molnupiravir. See Fact Sheet for Healthcare Providers: Emergency Use Authorization for Molnupiravir.

Corticosteroids: Because dexamethasone readily crosses the placenta, the RECOVERY RCT used prednisolone 40 mg daily by mouth or hydrocortisone 80 mg intravenously twice daily for pregnant participants.[141,142] Standard practice in maternal-fetal medicine at JHMI and elsewhere is to use dexamethasone when a corticosteroid is appropriate for COVID-19 management.

Tocilizumab: Though there are limited data regarding tocilizumab use in pregnant patients with COVID-19, more robust data exist regarding its use in patients with rheumatic conditions. One global analysis of 399 women and outcomes in 288 pregnancies found no substantial increased risk of fetal malformation.[143] A retrospective study from Japan that included 61 pregnancies in patients who received tocilizumab at conception found no increased rates of spontaneous abortion or congenital abnormalities.[144] Four pregnant women with refractory rheumatoid arthritis appeared to benefit without adverse outcomes.[145]

The use of tocilizumab in pregnant women with COVID-19 has been reported in small studies. For example, 12 women received tocilizumab in the second and third trimesters, with no apparent detrimental effects.[146] Additional case reports suggest successful outcomes in treating severe COVID-19 in pregnant patients.

Baricitinib and tofacitinib: There is no published literature regarding the use of these drugs for COVID-19 during pregnancy. Animal studies at doses in excess of the maximum human exposure have identified embryo-fetal toxicities, including skeletal anomalies and reduced fertility.[147] Experience regarding the use of these drugs in pregnancy is limited. There is one case report of a patient with rheumatoid arthritis who received baricitinib from conception through week 17 of pregnancy and delivered a healthy infant at 38 weeks.[148] Tofacitinib use in pregnancy is described among 60 patients without notable adverse outcomes compared with background rates.[149] (See also Reprotox > tofacitinib 2021.)

Fluvoxamine: Data on the use of fluvoxamine in pregnancy are limited, but it is "not thought to increase the risk of congenital abnormalities."[150] Because SSRI use in the third trimester has been associated with a small increase in pulmonary hypertension in newborns, clinicians should engage pregnant patients with COVID-19 in a discussion of the potential risks versus benefits of fluvoxamine treatment.

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

Box 4: 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) - Hydroxychloroquine (HCQ)* - Indomethacin or other nonsteroidal anti-inflammatory drugs (NSAIDs) - Ivermectin - Lopinavir/ritonavir - Nitazoxanide - Oseltamivir - Ribavirin - Umifenovir (not FDA-approved or available in the United States) - Vitamin C - Vitamin D - Zinc *Use of HCQ for treatment or prophylaxis of COVID-19 is prohibited at JHHS unless it is part of a clinical trial. Patients who may have been prescribed HCQ for prophylaxis as an outpatient should not continue therapy for prophylaxis as an inpatient unless part of a clinical trial.

There is no plausible evidence of or reported in vitro activity for the agents listed above, 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.[151] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression,[152] leading to concerns of a theoretical risk with 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.[153] The best evidence suggests similar or improved outcomes among people on chronic ACE or ARB therapy who develop COVID-19.[154]

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 compared 98 inpatients with COVID-19 who received aspirin to 314 who did not receive aspirin.[155] 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.[156] 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.[157] No clinical efficacy was found in a study of azithromycin against MERS-CoV.[158]

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).[159] Another RCT, with 4,488 ambulatory participants with COVID-19, 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.[160]

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.[161] 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.[161]

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.[162] 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 1 and phase 2 clinical trials and in compassionate use, and all have shown good tolerability.[163] 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.[164]

Favipiravir: This inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.[165,166] An open-label, non-RCT 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.[165] 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.[166] This drug is not approved by the FDA and is not available in the United States.

Hydroxychloroquine (HCQ): HCQ's *in vitro* activity against SARS-CoV-2 and some other viruses[167,168] 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.[169,170] Multiple RCTs, including those sponsored by the NIH, have been halted because of the futility of HCQ treatment or under-enrollment.[171-174]

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.[175]

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*.[176] 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.[177] 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.[178] 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.[179-183] 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.[184] 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.[185] 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.[183] 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.[185] There was no difference in symptom resolution between study arms. A systematic review has summarized additional retrospective and prospective studies (preprint).[181]

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).[186] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[187] 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.[188] 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.[189] 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.[190]

Nitazoxanide: This agent has been tested *in vitro* against MERS-CoV and SARS-CoV-2 and found to have activity.[191] 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.[192]

RBV: In a systematic review, RBV was not found to be beneficial against SARS-CoV-1.[193] In a multicenter observational study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[194]

Umifenovir: This agent was routinely used in China to treat patients with COVID-19.[195] 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.[196] In that trial, there was no difference in the primary endpoint of 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.[197] 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.[198] 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.[199] 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.[200]

VII. 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 5: COVID-19 Pharmacologic Treatment Guidance Writing Group

- **Chair:** Paul G. Auwaerter, MD, MBA, Clinical Director, Division of Infectious Diseases; Professor of Medicine
- **Lead author:** Christopher J. Hoffmann, MD, MPH, Associate Professor of Medicine, Department of Medicine, Division of Infectious Diseases
- **Editor:** Mary Beth Hansen, MA, JHU/NYSDOH Clinical Guidelines Program Director
- **Contributing members:**
  - Robin K. Avery, MD, Professor of Medicine
  - Richard F. Ambinder, MD, PhD, Director, Division of Hematologic Malignancies; Professor of Oncology
  - Andrew M. Cameron, MD, PhD, Chief, Division of Transplantation; Professor of Surgery
  - Larry W. Chang, MD, MPH, Associate Professor of Medicine, Department of Medicine, Division of Infectious Diseases
  - Natasha M. Chida, MD, MSPH, Associate Director, Infectious Diseases Fellowship Program; Assistant Professor of Medicine
  - Franco R. D'Alessio, MD, Assistant Professor of Medicine, Pulmonary and Critical Care Medicine
  - Rebecca H. Dezube, MD, MHS, Assistant Professor of Medicine, Pulmonary and Critical Care Medicine; Medical Director, COVID Faculty
  - Kate Dzintars, PharmD, Clinical Pharmacy Specialist, Division of Infectious Disease
  - Brian T. Garibaldi, MD, Director, Johns Hopkins Biocontainment Unit; Associate Professor of Medicine
  - Elisa Ignatius, MD, MSc, Fourth Year Fellow, Infectious Diseases, Clinical Pharmacology
  - Tania Jain, MBBS, Assistant Professor of Oncology
  - Andrew Karaba, MD, PhD, Assistant Professor of Medicine, Division of Infectious Diseases
  - Kieren Marr, MD, MBA, Director, Transplant and Oncology Infectious Diseases; Vice-Chair for Innovation in Healthcare Implementation, DOM; Professor of Medicine
  - Christian A. Merlo, MD, MPH, Director of Outpatient Clinical Operations, Associate Professor of Medicine
  - Pali D. Shah, MD, Medical Director, Johns Hopkins Lung Transplantation; Assistant Professor of Medicine
  - R. Scott Stephens, MD, Director, Oncology and Bone Marrow Transplant Critical Care; 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.

References

1. Yanes-Lane M, Winters N, Fregonese F, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. *PLoS One.* 2020;15(11):e0241536. https://pubmed.ncbi.nlm.nih.gov/33141862/
2. Sachithanandham J, Thio CL, Balagopal A. The natural history of severe acute respiratory syndrome coronavirus 2 infection: A composite but incomplete picture. *Clin Infect Dis.* 2020. https://pubmed.ncbi.nlm.nih.gov/33090197/
3. Young BE, Ong SWX, Ng LFP, et al. Viral dynamics and immune correlates of COVID-19 disease severity. *Clin Infect Dis.* 2020. https://pubmed.ncbi.nlm.nih.gov/32856707/
4. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med.* 2020;26(5):672-675. https://pubmed.ncbi.nlm.nih.gov/32296168/
5. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med.* 2020;180(9):1156-1163. https://pubmed.ncbi.nlm.nih.gov/32356867/
6. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe.* 2021;2(1):e13-e22. https://pubmed.ncbi.nlm.nih.gov/33521734/
7. Zayet S, Gendrin V, Klopfenstein T. Natural history of COVID-19: back to basics. *New Microbes New Infect.* 2020;38:100815. https://pubmed.ncbi.nlm.nih.gov/33204429/
8. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(24):759-765. https://pubmed.ncbi.nlm.nih.gov/32555134/
9. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32109013
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506. https://www.ncbi.nlm.nih.gov/pubmed/31986264
11. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ.* 2020;369:m1966. https://pubmed.ncbi.nlm.nih.gov/32444366/
12. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32091533
13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32171076
14. Cunningham JW, Vaduganathan M, Claggett BL, et al. Clinical outcomes in young US adults hospitalized with COVID-19. *JAMA Intern Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/32902580/
15. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. *PLoS Med.* 2020;17(9):e1003321. https://pubmed.ncbi.nlm.nih.gov/32911500/
16. Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. *Ann Intern Med.* 2020;173(10):773-781. https://pubmed.ncbi.nlm.nih.gov/32783686/
17. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. *J Med Virol.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32343429
18. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol.* 2020;146(1):128-136.e124. https://pubmed.ncbi.nlm.nih.gov/32425269/

19. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32217835

20. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med.* 2014;6(224):224ra225. https://www.ncbi.nlm.nih.gov/pubmed/24553386

21. Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A, Sadelain M. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med.* 2018;24(6):731-738. https://www.ncbi.nlm.nih.gov/pubmed/29808005

22. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med.* 2018;24(6):739-748. https://www.ncbi.nlm.nih.gov/pubmed/29808007

23. Sterner RM, Sakemura R, Cox MJ, et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood.* 2019;133(7):697-709. https://www.ncbi.nlm.nih.gov/pubmed/30463995

24. Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *National Science Review.* 2020:[Epub ahead of print]. https://doi.org/10.1093/nsr/nwaa041

25. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A.* 2020;117(20):10970-10975. https://pubmed.ncbi.nlm.nih.gov/32350134/

26. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32125452

27. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis.* 2020;20(6):697-706. https://pubmed.ncbi.nlm.nih.gov/32224310/

28. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32291094

29. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32268022

30. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32220112

31. Truong TT, Ryutov A, Pandey U, et al. Persistent SARS-CoV-2 infection and increasing viral variants in children and young adults with impaired humoral immunity. *medRxiv.* 2021. https://www.ncbi.nlm.nih.gov/pubmed/33688673

32. Nakajima Y, Ogai A, Furukawa K, et al. Prolonged viral shedding of SARS-CoV-2 in an immunocompromised patient. *J Infect Chemother.* 2021;27(2):387-389. https://www.ncbi.nlm.nih.gov/pubmed/33328135

33. He X, Lau EHY, Wu P, et al. Author Correction: Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med.* 2020;26(9):1491-1493. https://pubmed.ncbi.nlm.nih.gov/32770170/

34. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-271. https://www.ncbi.nlm.nih.gov/pubmed/32020029

35. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med.* 2017;9(396):eaal3653. https://www.ncbi.nlm.nih.gov/pubmed/28659436

36. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - Final report. *N Engl J Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/32445440/

37. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32459919

38. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients With moderate COVID-19: A randomized clinical trial. *JAMA.* 2020. https://pubmed.ncbi.nlm.nih.gov/32821939/

39. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. *N Engl J Med.* 2021;384(6):497-511. https://pubmed.ncbi.nlm.nih.gov/33264556/

40. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis.* 2021. https://www.ncbi.nlm.nih.gov/pubmed/34534511

41. Ohl ME, Miller DR, Lund BC, et al. Association of remdesivir treatment with survival and length of hospital stay among US veterans hospitalized with COVID-19. *JAMA Netw Open.* 2021;4(7):e2114741. https://www.ncbi.nlm.nih.gov/pubmed/34264329

42. Garibaldi BT, Wang K, Robinson ML, et al. Effectiveness of remdesivir with and without dexamethasone in hospitalized patients with COVID-19. 2020; https://doi.org/10.1101/2020.11.19.20234153. Accessed 2020 December 10.

43. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med.* 2021. https://pubmed.ncbi.nlm.nih.gov/34937145/

44. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2020:[Epub ahead of print]. https://doi.org/10.1016/S0140-6736(20)31022-9

45. Buckland MS, Galloway JB, Fhogartaigh CN, et al. Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report. *Nat Commun.* 2020;11(1):6385. https://www.ncbi.nlm.nih.gov/pubmed/33318491

46. Camprubi D, Gaya A, Marcos MA, et al. Persistent replication of SARS-CoV-2 in a severely immunocompromised patient treated with several courses of remdesivir. *Int J Infect Dis.* 2021;104:379-381. https://www.ncbi.nlm.nih.gov/pubmed/33359065

47. Kemp SA, Collier DA, Datir RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. *Nature.* 2021;592(7853):277-282. https://www.ncbi.nlm.nih.gov/pubmed/33545711

48. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? *Clin Infect Dis.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/33029620

49. Brown LK, Ruis C, Clark I, et al. A comprehensive characterization of chronic norovirus infection in immunodeficient hosts. *J Allergy Clin Immunol.* 2019;144(5):1450-1453. https://www.ncbi.nlm.nih.gov/pubmed/31415785

50. Hawkinson DJ, Ison MG. Respiratory viruses: influenza, RSV, and adenovirus in kidney transplantation. *Semin Nephrol.* 2016;36(5):417-427. https://www.ncbi.nlm.nih.gov/pubmed/27772626

51. Rao SN, Manissero D, Steele VR, Pareja J. A systematic review of the clinical utility of cycle threshold values in the context of COVID-19. *Infect Dis Ther.* 2020;9(3):573-586. https://www.ncbi.nlm.nih.gov/pubmed/32725536

52. Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro Surveill.* 2020;25(32). https://www.ncbi.nlm.nih.gov/pubmed/32794447

53. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - Preliminary report. *N Engl J Med.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32445440

54. European Medicines Agency. Veklury 100 mg concentrate for solution for infusion: Summary of product characteristics. 2020; https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf. Accessed 2020 December 15.

55. Thakare S, Gandhi C, Modi T, et al. Safety of remdesivir in patients with acute kidney injury or CKD. *Kidney Int Rep.* 2021;6(1):206-210. https://pubmed.ncbi.nlm.nih.gov/33073066/

56. Lilly CM, Welch VL, Mayer T, Ranauro P, Meisner J, Luke DR. Evaluation of intravenous voriconazole in patients with compromised renal function. *BMC Infect Dis.* 2013;13:14. https://pubmed.ncbi.nlm.nih.gov/23320795/

57. Luke DR, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). *J Pharm Sci.* 2010;99(8):3291-3301. https://pubmed.ncbi.nlm.nih.gov/20213839/

58. Kiser TH, Fish DN, Aquilante CL, et al. Evaluation of sulfobutylether-β-cyclodextrin (SBECD) accumulation and voriconazole pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. *Crit Care.* 2015;19(1):32. https://pubmed.ncbi.nlm.nih.gov/25645660/

59. Hoover RK, Alcorn H, Jr., Lawrence L, et al. Clinical pharmacokinetics of sulfobutylether-beta-cyclodextrin in patients with varying degrees of renal impairment. *J Clin Pharmacol.* 2018;58(6):814-822. https://www.ncbi.nlm.nih.gov/pubmed/29578585

60. Neofytos D, Lombardi LR, Shields RK, et al. Administration of voriconazole in patients with renal dysfunction. *Clin Infect Dis.* 2012;54(7):913-921. https://www.ncbi.nlm.nih.gov/pubmed/22267716

61. Oude Lashof AM, Sobel JD, Ruhnke M, et al. Safety and tolerability of voriconazole in patients with baseline renal insufficiency and candidemia. *Antimicrob Agents Chemother.* 2012;56(6):3133-3137. https://www.ncbi.nlm.nih.gov/pubmed/22450974

62. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol.* 2020;31(7):1384-1386. https://pubmed.ncbi.nlm.nih.gov/32513665/

63. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med.* 2021. https://pubmed.ncbi.nlm.nih.gov/34914868/

64. Garraud O, Heshmati F, Pozzetto B, et al. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. *Transfus Clin Biol.* 2016;23(1):39-44. https://www.ncbi.nlm.nih.gov/pubmed/26775794

65. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* 2015;211(1):80-90. https://www.ncbi.nlm.nih.gov/pubmed/25030060

66. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis.* 2005;24(1):44-46. https://www.ncbi.nlm.nih.gov/pubmed/15616839

67. Mustafa S, Balkhy H, Gabere MN. Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): A review. *J Infect Public Health.* 2018;11(1):9-17. https://www.ncbi.nlm.nih.gov/pubmed/28864360

68. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32254064

69. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. *JAMA.* 2020. https://pubmed.ncbi.nlm.nih.gov/32492084/

70. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19. A randomized clinical trial. *medRxiv.* 2020:2020.2007.2001.20139857. https://www.medrxiv.org/content/medrxiv/early/2020/07/03/2020.07.01.20139857.full.pdf

71. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med.* 2021. https://pubmed.ncbi.nlm.nih.gov/34504336/

72. Avendaño-Solá C, Ramos-Martínez A, Muñez-Rubio E, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. *J Clin Invest.* 2021. https://pubmed.ncbi.nlm.nih.gov/34473652/

73. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/33232588/

74. Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med.* 2021. https://pubmed.ncbi.nlm.nih.gov/33406353/

75. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early convalescent plasma for high-risk outpatients with Covid-19. *N Engl J Med.* 2021. https://pubmed.ncbi.nlm.nih.gov/34407339/

76. Writing Committee for the Remap- C. A. P. Investigators, Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA.* 2021. https://www.ncbi.nlm.nih.gov/pubmed/34606578

77. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. *N Engl J Med.* 2021;384(11):1015-1027. https://pubmed.ncbi.nlm.nih.gov/33523609/

78. Kunze KL, Johnson PW, van Helmond N, et al. Mortality in individuals treated with COVID-19 convalescent plasma varies with the geographic provenance of donors. *Nat Commun.* 2021;12(1):4864. https://pubmed.ncbi.nlm.nih.gov/34381030/

79. Arnold Egloff SA, Junglen A, Restivo JS, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. *J Clin Invest.* 2021. https://pubmed.ncbi.nlm.nih.gov/34464352/

80. Schmidt F, Muecksch F, Weisblum Y, et al. Plasma neutralization properties of the SARS-CoV-2 Omicron variant [Preprint]. *medRxiv.* 2021. https://www.medrxiv.org/content/medrxiv/early/2021/12/13/2021.12.12.21267646.full.pdf

81. Cele S, Gazy I, Jackson L, et al. Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. *Nature.* 2021. https://pubmed.ncbi.nlm.nih.gov/33780970/

82. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood.* 2019;133(17):1840-1853. https://www.ncbi.nlm.nih.gov/pubmed/30808638

83. Voelker MT, Spieth P. Blood transfusion associated lung injury. *J Thorac Dis.* 2019;11(8):3609-3615. https://www.ncbi.nlm.nih.gov/pubmed/31559068

84. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. *J Clin Invest.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32525844

85. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc.* 2020;95(9):1888-1897. https://pubmed.ncbi.nlm.nih.gov/32861333/

86. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/33113295/

87. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med.* 2021;385(15):1382-1392. https://www.ncbi.nlm.nih.gov/pubmed/34260849

88. Regeneron. Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hostpitalized COVID-19 patients. 2020; https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and. Accessed 2020 October 6.

89. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Preprint: Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. 2021. Accessed 2021 July 6.

90. Mylonakis E, Somersan-Karakaya S, Sivapalasingam S, et al. Casirivimab and imdevimab for treatment of hospitalized patients with COVID-19 receiving low flow or no supplemental oxygen. Abstract LB4. IDWeek; Sep 29 to Oct 3, 2021; Virtual.

91. Gupta G, Gonzalez-Rojas Y, Juarez E, et al. Early Covid-19 treatment with SARS-CoV-2 neutralizing antibody sotrovimab. 2021; https://doi.org/10.1101/2021.05.27.21257096. Accessed 2021 May 29.

92. FDA. Frequently asked questions on the emergency use authorization for bamlanivimab. 2020; https://www.fda.gov/media/143605/download. Accessed 2020 November 16.

93. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol.* 2004;31(1):69-75. https://www.ncbi.nlm.nih.gov/pubmed/15288617

94. Chan JF, Chan KH, Kao RY, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. *J Infect.* 2013;67(6):606-616. https://www.ncbi.nlm.nih.gov/pubmed/24096239

95. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32401715

96. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 - Preliminary report. *N Engl J Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/32678530/

97. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: An open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr.* 2021:Online ahead of print. https://pubmed.ncbi.nlm.nih.gov/33534047/

98. Jung C, Wernly B, Fjolner J, et al. Steroid use in elderly critically ill COVID-19 patients. *Eur Respir J.* 2021. https://www.ncbi.nlm.nih.gov/pubmed/34172464

99. Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. *JAMA.* 2020. https://pubmed.ncbi.nlm.nih.gov/32876694/

100. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: A potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA.* 2020;324(7):623-624. https://pubmed.ncbi.nlm.nih.gov/32761166/

101. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med.* 2021;9(7):763-772. https://www.ncbi.nlm.nih.gov/pubmed/33844996

102. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet.* 2021;398(10303):843-855. https://www.ncbi.nlm.nih.gov/pubmed/34388395

103. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med.* 2021;384(1):20-30. https://pubmed.ncbi.nlm.nih.gov/33332779/

104. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med.* 2021;384(16):1491-1502. https://pubmed.ncbi.nlm.nih.gov/33631065/

105. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2021;397(10285):1637-1645. https://pubmed.ncbi.nlm.nih.gov/33933206/

106. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med.* 2021;384(9):795-807. https://pubmed.ncbi.nlm.nih.gov/33306283/

107. Marconi VC, Ramanan AV, de Bono S, et al. Baricitinib plus standard of care for hospitalized adults with COVID-19 [Preprint]. 2021; https://doi.org/10.1101/2021.04.30.21255934. Accessed 2021 May 27.

108. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: Results from the live-air phase 3 randomized double-blind placebo-controlled trial [Preprint]. 2021; https://doi.org/10.1101/2021.05.01.21256470. Accessed 2021 May 27.

109. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/33085857/

110. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized clinical trial. *JAMA Intern Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/33080017/

111. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. *JAMA Intern Med.* 2020. https://pubmed.ncbi.nlm.nih.gov/33080005/

112. Mariette X, Hermine O, Tharaux PL, et al. Effectiveness of tocilizumab in patients hospitalized with COVID-19: A follow-up of the CORIMUNO-TOCI-1 randomized clinical trial. *JAMA Intern Med.* 2021. https://pubmed.ncbi.nlm.nih.gov/34028504/

113. Roche. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. 2020; https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Accessed 2020 Aug 10.

114. ClinicalTrials.gov. A study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACTA). 2021; https://clinicaltrials.gov/ct2/show/NCT04320615?term=COVACTA&draw=2&rank=1. Accessed 2020 Aug 10.

115. Roche. Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia. 2020; https://www.roche.com/media/releases/med-cor-2020-09-18.htm. Accessed 2020 October 6.

116. Sanofi. Press release: Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. 2020; https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00. Accessed 2020 Aug 10.

117. ClinicalTrials.gov. Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19. 2020; https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&cond=covid-19&draw=2. Accessed 2020 Aug 10.

118. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med.* 2021:Online ahead of print. https://pubmed.ncbi.nlm.nih.gov/33631065/

119. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ.* 2021;372:n84. https://pubmed.ncbi.nlm.nih.gov/33472855/

120. W. H. O. Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Shankar-Hari M, Vale CL, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA.* 2021. https://www.ncbi.nlm.nih.gov/pubmed/34228774

121. Parampalli Yajnanarayana S, Stubig T, Cornez I, et al. JAK1/2 inhibition impairs T cell function in vitro and in patients with myeloproliferative neoplasms. *Br J Haematol.* 2015;169(6):824-833. https://www.ncbi.nlm.nih.gov/pubmed/25824483

122. Eli Lilly and Company. Baricitinib in combination with remdesivir reduces time to recovery in hospitalized patients with COVID-19 in NIAID-sponsored ACTT-2 trial. 2020; https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery. Accessed 2020 October 7.

123. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med.* 2021. https://pubmed.ncbi.nlm.nih.gov/34480861/

124. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. *Blood.* 2017;130(21):2295-2306. https://www.ncbi.nlm.nih.gov/pubmed/28924019

125. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol.* 2020;2(6):e325-e331. https://pubmed.ncbi.nlm.nih.gov/32501454/

126. Khattri S, Zandman-Goddard G. Statins and autoimmunity. *Immunol Res.* 2013;56(2-3):348-357. https://www.ncbi.nlm.nih.gov/pubmed/23572428

127. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med.* 2013;368(16):1509-1518. https://www.ncbi.nlm.nih.gov/pubmed/23527958

128. Page TH, Urbaniak AM, Espirito Santo AI, et al. Bruton's tyrosine kinase regulates TLR7/8-induced TNF transcription via nuclear factor-kappaB recruitment. *Biochem Biophys Res Commun.* 2018;499(2):260-266. https://www.ncbi.nlm.nih.gov/pubmed/29567473

129. Florence JM, Krupa A, Booshehri LM, Davis SA, Matthay MA, Kurdowska AK. Inhibiting Bruton's tyrosine kinase rescues mice from lethal influenza-induced acute lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2018;315(1):L52-l58. https://www.ncbi.nlm.nih.gov/pubmed/29516781

130. Treon SP, Castillo J, Skarbnik AP, et al. The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients. *Blood.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32302379

131. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol.* 2020;5(48). https://pubmed.ncbi.nlm.nih.gov/32503877/

132. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA.* 2020;324(22):2292-2300. https://www.ncbi.nlm.nih.gov/pubmed/33180097

133. Reis G, Silva EA, Silva DC, et al. Preprint: Effect of early treatment with fluvoxamine on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial. 2021; https://doi.org/10.1101/2021.08.19.21262323, 2021 September 14.

134. Galeotti C, Kaveri SV, Bayry J. IVIG-mediated effector functions in autoimmune and inflammatory diseases. *Int Immunol.* 2017;29(11):491-498. https://www.ncbi.nlm.nih.gov/pubmed/28666326

135. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med.* 2006;3(9):e343. https://www.ncbi.nlm.nih.gov/pubmed/16968120

136. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis.* 2020;7(3):ofaa102. https://pubmed.ncbi.nlm.nih.gov/32258207/

137. FDA. Emergency use authorization (EUA) of REGEN-COV (casirivimab and imdevimab). 2021; https://www.fda.gov/media/145611/download. Accessed 2021 September 10.

138. FDA. Emergency use authorization (EUA) of VEKLURY (remdesivir) for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. 2020; https://www.fda.gov/media/137566/download. Accessed 2021 September 10.

139. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate use of remdesivir in pregnant women with severe Covid-19. *Clin Infect Dis.* 2020. https://pubmed.ncbi.nlm.nih.gov/33031500/

140. Jorgensen SCJ, Davis MR, Lapinsky SE. A review of remdesivir for COVID-19 in pregnancy and lactation. *J Antimicrob Chemother.* 2021. https://pubmed.ncbi.nlm.nih.gov/34427297/

141. Temprano KK, Bandlamudi R, Moore TL. Antirheumatic drugs in pregnancy and lactation. *Semin Arthritis Rheum.* 2005;35(2):112-121. https://pubmed.ncbi.nlm.nih.gov/16194696/

142. Lekarev O, New MI. Adrenal disease in pregnancy. *Best Pract Res Clin Endocrinol Metab.* 2011;25(6):959-973. https://pubmed.ncbi.nlm.nih.gov/22115169/

143. Hoeltzenbein M, Beck E, Rajwanshi R, et al. Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data. *Semin Arthritis Rheum.* 2016;46(2):238-245. https://pubmed.ncbi.nlm.nih.gov/27346577/

144. Nakajima K, Watanabe O, Mochizuki M, Nakasone A, Ishizuka N, Murashima A. Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. *Mod Rheumatol.* 2016;26(5):667-671. https://pubmed.ncbi.nlm.nih.gov/26873562/

145. Kaneko K, Sugitani M, Goto M, Murashima A. Tocilizumab and pregnancy: Four cases of pregnancy in young women with rheumatoid arthritis refractory to anti-TNF biologics with exposure to tocilizumab. *Mod Rheumatol.* 2016;26(5):672-675. https://pubmed.ncbi.nlm.nih.gov/26872426/

146. Jiménez-Lozano I, Caro-Teller JM, Fernández-Hidalgo N, et al. Safety of tocilizumab in COVID-19 pregnant women and their newborn: A retrospective study. *J Clin Pharm Ther.* 2021;46(4):1062-1070. https://pubmed.ncbi.nlm.nih.gov/33638257/

147. FDA. Emergency use authorization (EUA) of baricitinib. 2021; https://www.fda.gov/media/143823/download. Accessed 2021 September 10.

148. Costanzo G, Firinu D, Losa F, Deidda M, Barca MP, Del Giacco S. Baricitinib exposure during pregnancy in rheumatoid arthritis. *Ther Adv Musculoskelet Dis.* 2020;12:1759720x19899296. https://pubmed.ncbi.nlm.nih.gov/32071617/

149. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis.* 2018;24(12):2494-2500. https://pubmed.ncbi.nlm.nih.gov/29982686/

150. NIH. COVID-19 Treatment Guidelines: Flovoxamine Considerations in Pregnancy. 2021; https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/fluvoxamine/. Accessed 2021 November 16.

151. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32142651

152. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation.* 2005;111(20):2605-2610. https://www.ncbi.nlm.nih.gov/pubmed/15897343

153. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med.* 2020;382(17):1653-1659. https://pubmed.ncbi.nlm.nih.gov/32227760/

154. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32302265

155. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use Is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. *Anesth Analg.* 2021;132(4):930-941. https://pubmed.ncbi.nlm.nih.gov/33093359/

156. PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet.* 2021;397(10279):1063-1074. https://pubmed.ncbi.nlm.nih.gov/33676597/

157. Lane JCE, Weaver J, Kostka K, et al. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. *Lancet Rheumatol.* 2020;2(11):e698-e711. https://pubmed.ncbi.nlm.nih.gov/32864627/

158. Arabi YM, Deeb AM, Al-Hameed F, et al. Macrolides in critically ill patients with Middle East Respiratory Syndrome. *Int J Infect Dis.* 2019;81:184-190. https://www.ncbi.nlm.nih.gov/pubmed/30690213

159. Lopes MI, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. *RMD Open.* 2021;7(1). https://pubmed.ncbi.nlm.nih.gov/33542047/

160. Tardif J-C, Bouabdallaoui N, L'Allier PL, et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. *medRxiv.* 2021:2021.2001.2026.21250494. https://www.medrxiv.org/content/medrxiv/early/2021/01/27/2021.01.26.21250494.full.pdf

161. De Meyer S, Bojkova D, Cinatl J, et al. Lack of antiviral activity of darunavir against SARS-CoV-2. *Int J Infect Dis.* 2020;97:7-10. https://pubmed.ncbi.nlm.nih.gov/32479865/

162. Qing E, Hantak M, Perlman S, Gallagher T. Distinct roles for sialoside and protein receptors in coronavirus infection. *mBio.* 2020;11(1). https://www.ncbi.nlm.nih.gov/pubmed/32047128

163. Guzman-Suarez BB, Buckley MW, Gilmore ET, et al. Clinical potential of DAS181 for treatment of parainfluenza-3 infections in transplant recipients. *Transpl Infect Dis.* 2012;14(4):427-433. https://www.ncbi.nlm.nih.gov/pubmed/22340538

164. Borrell B. New York clinical trial quietly tests heartburn remedy against coronavirus. 2020; https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus. Accessed 2020 April 27.

165. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: An open-label control study. *Engineering (Beijing).* 2020. https://pubmed.ncbi.nlm.nih.gov/32346491/

166. Chen C, Zhang Y, Huang J, et al. Favipiravir versus arbidol for clinical recovery rate in moderate and severe adult COVID-19 patients: a prospective, multicenter, open-label, randomized controlled clinical trial. *Front Pharmacol.* 2021;12:683296. https://pubmed.ncbi.nlm.nih.gov/34539392/

167. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32150618

168. Barnard DL, Hubbard VD, Burton J, et al. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARSCoV) by calpain inhibitors and beta-D-N4-hydroxycytidine. *Antivir Chem Chemother.* 2004;15(1):15-22. https://www.ncbi.nlm.nih.gov/pubmed/15074711

169. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients With COVID-19 in New York State. *JAMA.* 2020. https://pubmed.ncbi.nlm.nih.gov/32392282/

170. Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ.* 2020;369:m1844. https://pubmed.ncbi.nlm.nih.gov/32409486/

171. NIAID. Bulletin—NIH clinical trial evaluating hydroxychloroquine and azithromycin for COVID-19 closes early. 2020; https://www.niaid.nih.gov/news-events/bulletin-nih-clinical-trial-evaluating-hydroxychloroquine-and-azithromycin-covid-19. Accessed 2020 June 22.

172. Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: A randomized clinical trial. *JAMA.* 2020;324(21):2165-2176. https://pubmed.ncbi.nlm.nih.gov/33165621/

173. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med.* 2020;383(21):2041-2052. https://pubmed.ncbi.nlm.nih.gov/32706953/

174. Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* 2020;383(21):2030-2040. https://pubmed.ncbi.nlm.nih.gov/33031652/

175. FDA. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. 2020; https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Accessed 2020 June 22.

176. Amici C, Di Caro A, Ciucci A, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. *Antivir Ther.* 2006;11(8):1021-1030. https://www.ncbi.nlm.nih.gov/pubmed/17302372

177. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32171062

178. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020;178:104787. https://pubmed.ncbi.nlm.nih.gov/32251768/

179. Camprubí D, Almuedo-Riera A, Martí-Soler H, et al. Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients. *PLoS One.* 2020;15(11):e0242184. https://pubmed.ncbi.nlm.nih.gov/33175880/

180. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The ICON study. *Chest.* 2020. https://pubmed.ncbi.nlm.nih.gov/33065103/

181. Kalfas S, Visvanathan K, Chan K, Drago J. The therapeutic potential of ivermectin for COVID-19: A systematic review of mechanisms and evidence. 2020; https://doi.org/10.1101/2020.11.30.20236570. Accessed 2020 December 11.

182. Gorial FI, Mashhadani S, Sayaly HM, et al. Effectiveness of ivermectin as add-on therapy in COVID-19 management (pilot trial). 2020; https://doi.org/10.1101/2020.07.07.20145979. Accessed 2020 December 11.

183. Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. 2020; https://doi.org/10.1101/2020.10.26.20219345. Accessed 2020 December 11.

184. López-Medina E, López P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: A randomized clinical trial. *JAMA.* 2021. https://pubmed.ncbi.nlm.nih.gov/33662102/

185. Ahmed S, Karim MM, Ross AG, et al. A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis.* 2020. https://pubmed.ncbi.nlm.nih.gov/33278625/

186. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med.* 2020:[Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/32187464

187. Yan D, Liu XY, Zhu YN, et al. Factors associated with prolonged viral shedding and impact of lopinavir/ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection. *Eur Respir J.* 2020;56(1). https://pubmed.ncbi.nlm.nih.gov/32430428/

188. Ye XT, Luo YL, Xia SC, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of coronavirus disease 2019. *Eur Rev Med Pharmacol Sci.* 2020;24(6):3390-3396. https://www.ncbi.nlm.nih.gov/pubmed/32271456

189. Li Y, Xie Z, Lin W, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: An exploratory randomized controlled trial. *Med (N Y).* 2020. https://pubmed.ncbi.nlm.nih.gov/32838353/

190. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2020;396(10259):1345-1352. https://pubmed.ncbi.nlm.nih.gov/33031764/

191. Cao J, Forrest JC, Zhang X. A screen of the NIH Clinical Collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Res.* 2015;114:1-10. https://www.ncbi.nlm.nih.gov/pubmed/25451075

192. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32031570

193. Momattin H, Mohammed K, Zumla A, Memish ZA, Al-Tawfiq JA. Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)--possible lessons from a systematic review of SARS-CoV therapy. *Int J Infect Dis.* 2013;17(10):e792-798. https://www.ncbi.nlm.nih.gov/pubmed/23993766

194. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East Respiratory Syndrome: A multicenter observational study. *Clin Infect Dis.* 2019. https://www.ncbi.nlm.nih.gov/pubmed/31925415

195. China National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). 2020; http://kjfy.meetingchina.org/msite/news/show/cn/3337.html. Accessed 2020 March 21.

196. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI randomized clinical trial. *JAMA.* 2019;322(13):1261-1270. https://www.ncbi.nlm.nih.gov/pubmed/31573637

197. Dancer RC, Parekh D, Lax S, et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax.* 2015;70(7):617-624. https://pubmed.ncbi.nlm.nih.gov/25903964/

198. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among

patients hospitalized for COVID-19: A pilot randomized clinical study. *J Steroid Biochem Mol Biol.* 2020;203:105751. https://pubmed.ncbi.nlm.nih.gov/32871238/

199. Murai IH, Fernandes AL, Sales LP, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: A randomized clinical trial. *JAMA.* 2021. https://pubmed.ncbi.nlm.nih.gov/33595634/

200. Hemila H. Zinc lozenges may shorten the duration of colds: a systematic review. *Open Respir Med J.* 2011;5:51-58. https://www.ncbi.nlm.nih.gov/pubmed/21769305

Appendix A: Comparison of Selected Studies of Targeted Immunosuppression

Table A: 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) • 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) • 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% • RDV: 18.9%	No data	• CS: 94% • RDV: 72% • CS + RDV: 69%	• CS: 80% TOCI; 87% PBO • RDV: 52% TOCI; 5% PBO	• CS: 93% (after 6/17/20) • RDV: 31%	CS: 74% 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 • 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) • In-hospital mortality 27% TOCI v. 22% SARI v. 36% control	28-day hospital discharge: 57% TOCI v. 50% SOC (RR 1.22; CI 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) • 28-day mortality: 5% BARI/RDV v. 8% PBO/RDV (HR 0.65; 95% CI 0.39-1.09) • 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 • SAE: 15% TOCI; 20% PBO • No mortality difference	—	Survival and clinical improvement seen regardless of clinical stage

Table A: 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:

1. Marconi VC, Ramanan AV, de Bono S, et al. Baricitinib plus standard of care for hospitalized adults with COVID-19 [Preprint]. https://doi.org/10.1101/2021.04.30.21255934. Published 2021. Updated 2021 May 3. Accessed 2021 May 27.
2. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med*. 2021;384(9):795-807. https://pubmed.ncbi.nlm.nih.gov/33306283/.
3. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: Results from the live-air phase 3 randomized double-blind placebo-controlled trial [Preprint]. https://doi.org/10.1101/2021.05.01.21256470. Published 2021. Updated 2021 May 5. Accessed 2021 May 27.
4. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. https://pubmed.ncbi.nlm.nih.gov/33332779/.
5. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384(16):1491-1502. https://pubmed.ncbi.nlm.nih.gov/33631065/.
6. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. https://pubmed.ncbi.nlm.nih.gov/33933206/.

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%) • Fever, itching and hives are the most common mild symptoms • Low blood pressure, difficulty breathing, and organ injury are more serious but also much less common	• Before being given, ○ except in life-threatening emergencies, donated plasma is matched with your blood type ○ you may be given medicine • You will be monitored for any symptoms and the administration will be stopped if necessary
Infection: (less than 0.1%) • Bacteria • Viruses • Parasites • Prions	• Donors are screened prior to being allowed to give blood and all donated blood is carefully tested by suppliers before being sent to the hospital.

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

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

For Patient/Family

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

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

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

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)*

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