JHMI Clinical Recommendations for Pharmacologic Treatment of COVID-19

Updated 1/27/2023 and replaces the version of 1/20/2023; 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 1/27/2023 Update

Updates to Appendix C: Non-Oncology Remdesivir Infusion Ambulatory Referral Workflow **noted below:**

- Remdesivir is contraindicated in patients liver enzymes (AST/ALT/Alkaline Phosphatase) greater than ten times the upper limit of normal.
- The FDA warns of use of remdesivir for patients with GFR<30ml/min. JHM experience is that remdesivir is safe in CKD, including those on dialysis. A conversation of the risks/benefits of remdesivir with such patients should be documented in the therapy plan.

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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
Limited to Hospitalized Patients With Mild to Moderate COVID-19 and No Supplemental Oxygen Requirement, Not Originally Admitted for COVID-19 [a]		
Remdesivir	• ≤7 days new symptoms consistent with COVID-19 (fever, chills, dyspnea, cough, pharyngitis, myalgia, diarrhea, vomiting, or dysgeusia or anosmia) • At risk for severe COVID-19 [b] • Ineligible if O_2 required for COVID-19	• Order through EPIC. • Patients must meet criteria in Table 3. • 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 immunocompromised patients, clinicians may consider adding convalescent plasma.
Nirmatrelvir/ritonavir (Upon discharge, ensure that any patient who has not yet completed 5 days of treatment is given their dose-pack to complete the treatment course at home. *Do not send a new prescription to pharmacy.* See Appendix B: Paxlovid Formulary Addition)	• ≤5 days of symptoms • ≥12 years old • Mild to moderate COVID-19 • Patients not admitted for COVID-19 per se • At risk for severe COVID-19 [b] • Ineligible if O_2 required for COVID-19	• Substantial drug-drug interactions with ritonavir up to 2 weeks after the last dose; consult drug interaction databases and/or a clinical pharmacist as necessary. • Use is *not recommended* for patients taking tacrolimus or other calcineurin inhibitors, even if held during antiviral use. • Limited data suggest safe in pregnancy. • For immunocompromised patients, clinicians may consider adding convalescent plasma.
Molnupiravir (Not currently available within JHHS)	• ≤5 days of symptoms • ≥18 years old • Nonsevere, noncritical COVID • At risk for severe COVID-19 [b] • Unvaccinated or unlikely to respond to vaccine	Teratogenicity and mutagenicity concerns in pregnancy.

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**
	• Ineligible if O_2 required for COVID-19	
Patients Hospitalized With Progressive COVID-19 Disease		
Dexamethasone	• Supplemental O_2 required • Intensive care use allowed	• Use in pregnant patients same as in the nonpregnant. • Before treating patients with sickle cell disease, discuss use with the JH Sickle Cell Disease team.
Tocilizumab	• Supplemental O_2 required, high flow *or* intensive care ≤24 hours • CRP >7.5 if immunocompetent	• Use in combination with dexamethasone. • P&T chair or designee approval is required. • For immunocompromised patients, P&T approval does not require CRP. • May consider use in pregnancy.
Baricitinib	• Supplemental O_2 is required. • Intensive care ≤24 hours is allowed.	• If tocilizumab is unavailable or contraindicated or dexamethasone is contraindicated. • P&T chair or designee approval is required. • Animal study concerns for use in pregnancy.
Anakinra	• Supplemental O_2 is required. • Intensive care ≤24 hours is allowed.	• If tocilizumab and baricitinib are unavailable or contraindicated. • Use in combination with dexamethasone. • P&T chair or designee approval is required.
Limited to Patients with Compromised Immune Status		
Convalescent plasma (Limited supply of high titer units)	• For patients who are immunosuppressed or receiving immunosuppressive therapy. • Response appears to be better early in disease course. • Any O_2 requirement is allowed.	• Concomitant therapy with RDV may be beneficial for severely immunocompromised patients. • High titer required to neutralize Omicron variants. • May be used in conjunction with RDV in selected patients. • May consider use in pregnancy (if identical ABO match). • Blood type mismatch (compatible) units are allowed, but the infusions are limited to 1 unit/per day in non-pregnant patients.

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
Remdesivir	• Immunocompromised [c] • Any O_2 requirement is allowed. • Intensive care use is allowed.	• ID attending approval is required if the patient does not meet the criteria for RDV treatment (see row 1, above and Table 3 notes for details). • May consider use in pregnancy. • Concomitant therapy with convalescent plasma may be beneficial for severely immunocompromised patients.

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; O_2, oxygen; PCR, polymerase chain reaction; P&T, Pharmacy & Therapeutics Committee; RDV, remdesivir.

Notes:

a. If supply is available and the 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. 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); receiving rituximab or other anti-CD20-based treatment). Patients must have ≤21 days since COVID-19 symptom onset or first SARS-CoV-2 PCR test (current COVID-19–related symptoms are not necessary), or if >21 days since COVID-19 symptom onset or first SARS-CoV-2 PCR test, the patient must have a SARS-CoV-2 RT-PCR test 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).

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Table 2: Summary of 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, in order of preference	Authorized Use	Comments
Patients Early in COVID-19 Disease Course		
Nirmatrelvir/ritonavir (Check COVID-19 therapeutic locator for retail pharmacies)	• ≤5 days of symptoms, mild-moderate COVID-19 • ≥12 years old • Unvaccinated or unlikely to respond to vaccine *or*	• Preferred ambulatory treatment for COVID-19 • Substantial drug-drug interactions with ritonavir up to 2 weeks after the last dose; consult with drug interaction checker before use (e.g., Liverpool COVID-19 Drug Interactions Checker) or clinical pharmacist as necessary.

Table 2: Summary of 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, in order of preference	**Authorized Use**	**Comments**
	• At risk for severe COVID-19 [a]	• Use is *not recommended* for patients taking tacrolimus or other calcineurin inhibitors, even if those agents are held during antiviral use. • The CDC issued an alert regarding possible mild rebound symptoms and increased viral RNA shedding after treatment completion. • For pharmacies, see COVID-19 Therapeutics Locator. • Limited data suggest safe in pregnancy. • For highly immunocompromised patients, clinicians may consider adding convalescent plasma.
Remdesivir (3-day course)	• ≤7 days symptoms • At risk for severe COVID-19 [a] • Not for use with eGFR <30ml/min or AST or ALT >5x ULN in ambulatory setting	• Preferred, if nirmatrelvir/ritonavir is unavailable or contraindicated. • Administered as daily IV infusion x 3 days. • For immunocompromised patients, clinicians may consider adding convalescent plasma. • May consider use in pregnancy. • The preferred option is to refer the patient to the Baltimore Convention Center Field Hospital (complete the referral online); also available is the Takoma Park Adventist Outpatient Infusion Center. • If the Field Hospital has no capacity, order the infusion through an oncology therapy plan (only by Oncology attendings for oncology patients) or non-oncology therapy plan (for all other adults) and email the order to adultivinfusion@jhmi.edu for weekday infusion at the East Baltimore Park Infusion Center and to the Weinberg urgent care center on weekends. • See Appendix C: Non-Oncology Remdesivir Referral Workflow • Due to infusion capacity concerns, patients may be prioritized based on risks for severe COVID-19 (e.g., B cell disorders, solid organ transplant patients, vaccine-non-responders).
Convalescent plasma (Limited supply of high titer units)	• Immunosuppressed only • Response may be better early in disease.	• High titer units are required to neutralize Omicron variants (compatible ABO match). • May consider use in pregnancy (only identical ABO match units). • For highly immunocompromised patients, clinicians may consider adding nirmatrelvir/ritonavir (or if contraindicated, then use 3 days remdesivir IV or molnupiravir).
Molnupiravir (Available through dedicated retail pharmacies)	• ≤5 days of symptoms • ≥18 years old • Unvaccinated or unlikely to respond to vaccine *or*	• Has less clinical efficacy than nirmatrelvir/ritonavir. • See COVID-19 Therapeutics Locator for availability. • For an additional resource, see COVID-19 Public Therapeutic Locator [this page can be accessed only within the JHMI network].

Table 2: Summary of 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, in order of preference	**Authorized Use**	**Comments**
	• At risk for severe COVID-19 [a] • If paxlovid, mAbs, and RDV are not available or contraindicated.	• Teratogenicity and mutagenicity concerns for use in pregnancy.
Limited to Patients With Compromised Immune Status [b]		
Convalescent plasma (Limited supply of high-titer units)	Response may be better early in disease	• High titer is required to neutralize Omicron (compatible ABO match). • May consider use in pregnancy (only identical ABO match units). • For highly immunocompromised patients, clinicians may consider adding nirmatrelvir/ritonavir (or if contraindicated, then use 3 days remdesivir or 5 days if moderately or severely immunocompromised (may wish to consult with transplant oncology infectious diseases attending) or prescribe molnupiravir).

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; ED, emergency department; IV, intravenous; JHMI, Johns Hopkins Medical Institutions; MD, Maryland; O_2, oxygen.
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-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); receiving rituximab or other anti-CD20-based treatment).

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Box 2: Use With Caution in Neutropenic Patients With COVID-19
Granulocyte colony-stimulating factor (G-CSF; filgrastim): An observational study reported a 3-fold increase in hospitalization among patients with cancer with acute COVID-19 who received G-CSF for bone marrow support.[1]

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 inpatients and outpatients 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 Johns Hopkins Medical Institutions (JHMI) therapeutic protocols for COVID-19:** See Therapeutic Protocols for Hospitalized Patients and Therapeutic Protocols for Ambulatory Patients
- **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) COVID-19 Treatment Guidelines.

Box 3: 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)
- 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 individuals infected with SARS-CoV-2. This is most likely due to multiple factors that include but are not limited to age, comorbidities, vaccination status, exposure inoculum, and genetics. Between 0.25% and 40% of individuals infected with SARS-CoV-2 have asymptomatic or subclinical infection.[2] Onset of symptomatic disease typically occurs within 4 to 5 days (median) of exposure,[3] though this is likely shorter with the Omicron variant.[4] It appears that the peak level of viremia is reached at about the time of symptom onset, with high viremia lasting from 3 days prior until approximately 6 days after symptom onset, with no detectable viable virus 10 days after symptom onset in normal hosts. However, the period of viral shedding is lower in vaccinated people by about 2 days and the period of shedding is different with each viral variant.[5,6] Furthermore, RNA shedding lasts more than 2 weeks and can last months in immunocompromised hosts.[5,7-10] With the Omicron variant, the peak of viral shedding may occur later (day 2 of symptoms) and may persist longer (6-7 days after symptom onset).[11] Infectivity parallels high viral carriage. The period of contagiousness starts 2 to 5 days before symptom onset and extends to approximately 5 to 7 days after symptom onset depending on host and virus factors.

Symptomatic infection: Headache, myalgia, upper respiratory symptoms, sore throat, smell and/or taste abnormalities, and nausea and vomiting are typical initially and may be followed a few days later by fever, cough, diarrhea, and anosmia.[12] Overall, any 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 to 10 days of symptoms. Infection with the Omicron variant appears to cause more symptomatic infections, but symptoms are more often mild.[13]

Severe disease: Early in the epidemic, more severe disease leading to hospitalization occurred at a mean of 7 days after symptom onset, when the exudative diffuse alveolar damage stage gives way to the organizing pneumonia stage.[12,14-16] It is possible that Omicron and subsequent variants will have a different pattern of progression. 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.[17,18] 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, unvaccinated status, and possibly residence in a long-term care facility.[19-24]

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);[25,26] 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-18,[27] and IL-2R; granulocyte-macrophage colony-stimulating factor (GM-CSF); and tumor necrosis factor-alpha (TNF-α), all of which decline as patients recover.[28] Lymphopenia has also been reported, with declines in CD4+ and CD8+ T cells.[28] 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), but levels are often much lower in COVID-19.[29-36] Patients may progress to multiorgan failure as a result of cytokine-mediated hyperinflammation.[37]

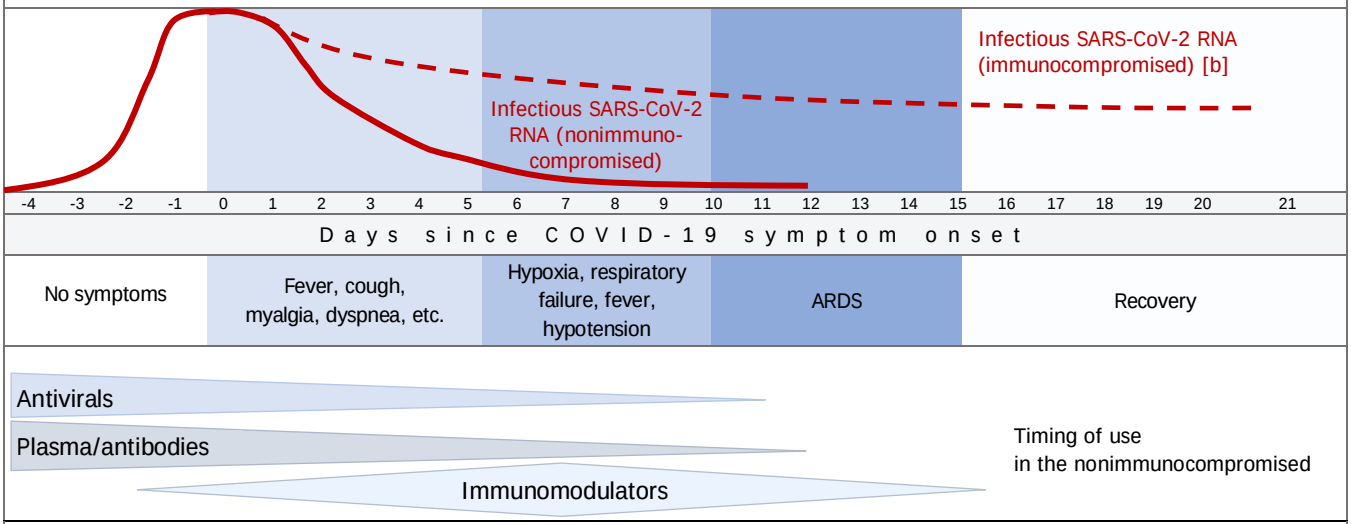
Additional complications: COVID-19 is a system disease and can lead to complications in multiple organ systems, including (1) arrhythmias and myocardial damage that can lead to heart failure and cardiogenic shock[38]; (2) stroke, seizure, meningoencephalitis, and Guillain-Barré syndrome[38]; (3) micro and macrovascular thrombosis, as well as venous thromboembolism in the periphery and the pulmonary vasculature[39-42]; and (4) multisystem inflammatory syndrome in children and adults (MIS-C and MIS-A). MIS-C and MIS-A are separate clinical entities from the hyperinflammatory syndrome. This complication is rare and presents 2 to 12 weeks after acute COVID-19. It is characterized by severe extrapulmonary organ dysfunction, often involving the heart, and elevated inflammatory markers and cytokines in the absence of significant respiratory disease.[43,44]

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 noninfectious 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-CoV-2 RNA levels in individuals who are and are not immunocompromised. [a]



Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

Notes:

a. Viral variants may have a longer period of infectious virus, i.e., >10 days in normal hosts.[5,7,9,10,45-47]

b. In immunocompromised individuals, duration is variable, especially in those who are 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 [IFN]).

☐ Remdesivir

Remdesivir (RDV) is an intravenous antiviral medication that has in vitro activity against SARS-CoV-2 and other coronaviruses.[48,49]

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 (SaO_2) <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).[50] 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 SaO_2 ≥94% on room air); exclusion criteria included mechanical ventilation or ECMO.[51] 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 participants in the 5-day arm and 17% in the 10-day arm 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.[52]

The SOLIDARITY study was a pragmatic, open-label RCT of RDV, hydroxychloroquine, lopinavir/ritonavir, and subcutaneous IFN beta 1a.[53] 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 (n=2,750), or hydroxychloroquine (n=954), lopinavir/ritonavir (n=1,411), lopinavir/ritonavir plus IFN (n=651), IFN alone (n=1,412), or no study drug (n=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 for any duration of time since symptom onset.[54] 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 on 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.[55] 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 JHMI suggests improved outcomes among participants who received RDV compared with matched participants who did not.[56]

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 on day 1 and 100 mg on days 2 and 3) with placebo among unvaccinated ambulatory patients ≥12 years old who had at least 1 risk factor for severe COVID-19 and ≤7 days of symptoms.[57] Characteristics among the 279 participants who received RDV and the 283 participants who received placebo were balanced, with a mean age of 50 years, 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 participants (0.7%) had a COVID-19-related hospitalization compared with 15 (5.3%) in the placebo arm (P=.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 among patients who:

- Are ≥12 years old and weigh ≥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):
  - Body mass index (BMI) ≥25 kg/m^2
  - Chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2)
  - 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 and 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).[58] 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.[58] 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 ratio, 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 patients with COVID-19 who are 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.[45,46,59-62] This effect is analogous to other acute viral infections (e.g., influenza, norovirus, respiratory syncytial virus) in patients with substantial immunodeficiency.[63,64] 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,[59,60] 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.[59,65,66] Integrating Ct values into the clinical assessment may offer supportive evidence of ongoing SARS-CoV-2 replication causing disease (e.g., Ct ≤30 cycles).[59,66] 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 nonimmunocompromised populations.[59,60] In some cases, the duration may be much longer than 21 days. The nonstandardized 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.

To enhance viral clearing, clinicians may consider combination treatment with RDV or nirmatrelvir/ritonavir (or molnupiravir if neither nimtrelavir/ritonavir nor RDV is possible) plus high-titer convalescent plasma for immunocompromised patients previously treated with these agents. The rationale is based on growing evidence in highly immunosuppressed patients that resistance may develop to the SARS-CoV-2 protease inhibitor and risks for prolonged viral carriage without combination therapy. There is no robust clinical data to back a formal recommendation; however, some limited case descriptions and animal model data suggest an efficacious approach.[67,68]

Adverse events: Adverse events from RDV or COVID-19 reported in clinical trials[50,51] 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[50,51] 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.[50,58] In the latter, there was no significant difference in effectiveness between 5 days and 10 days of RDV treatment. A higher proportion of participants in the 5-day treatment arm were discharged from the hospital and a higher proportion in the 5-day arm had improved symptom

scale by day 14. There were more serious adverse events (SAEs) in the 10-day 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 the 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.[69] Clinicians are advised to review potential drug-drug interactions with a clinical pharmacologist.

Considerations for use with impaired kidney function: RDV is eliminated primarily (49%) in the urine as an active metabolite, GS-441524, and only 10% as RDV (see FDA > Highlights of Prescribing Information for RDV). Clinical trials of COVID-19 treatment have excluded participants with an eGFR <30 mL/min/1.73 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/1.73 m^2 unless the potential benefit outweighs the potential risk.

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.[70] A case series of 46 patients with end-stage renal disease on dialysis or with a range of CKD stages who received RDV did not identify any increased risk of adverse effects or further renal impairment.[71] 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.[72-78]

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 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.

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 the 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*	• 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.

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
	documented sustained respiratory rate ≥24 breaths per minute • Mechanical ventilation or ECMO but only within the first 24 hours	• Patients with impaired kidney function: If eGFR <30 mL/min/1.73 m^2, 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 antibody therapy: Treatment with convalescent plasma is recommended. This may increase the probability of control of viral replication. • 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/1.73 m^2, 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 infection AND not previously treated with sotrovimab)	• Must have new (within the 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 • Meets the EUA criteria for nirmatrelvir/ritonavir treatment, but it is	• Treatment duration: 3 days • If the patient has 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 hepatotoxicity, RDV must be discontinued. • Patients with impaired kidney function: If eGFR <30 mL/min/1.73 m^2, medical record documentation of risk vs. benefits discussion with the patient and patient consent to RDV treatment is required. [d]

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
	contraindicated or not available per JHHS formulary.	• Patients are not to be admitted solely for RDV infusion.

Abbreviations: ALT, alanine transaminase; COVID-19; coronavirus disease 2019; CYP3A4, cytochrome P450 3A4; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; HCGH, Howard County General Hospital; ID, infectious diseases; JHBMC, Johns Hopkins Bayview Medical Center; JHACH, Johns Hopkins All Children's Hospital; JHH, Johns Hopkins Hospital; JHHS, Johns Hopkins Health System; JHMI, Johns Hopkins Medical Institutions; O_2, oxygen; PCR, polymerase chain reaction; SaO_2, oxygen saturation; SH, Suburban Hospital; SMH, Sibley Memorial Hospital; RDV, remdesivir; RT-PCR, 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.

3/8/2022

☐ 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 with ≤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 with 66 (6.3%) in the placebo arm (relative

risk reduction, 88%; *P*=.001). No deaths occurred in the nirmatrelvir arm and 12 occurred in the placebo arm. Adverse events were overall lower in the nirmatrelvir arm.

COVID-19 rebound: Post-trial reports and post-hoc analysis of trial data have identified viral RNA rebound and rebound of symptoms in some individuals treated with nirmatrelvir/ritonavir. On May 24, 2022, the Centers for Disease Control and Prevention (CDC) issued an alert on the possibility of a brief return of COVID-19 symptoms 2 to 8 days after therapy completion and a return of detectable viral RNA. The rebound appears to cause mild disease; there are no reports of rebound-associated severe disease. In the EPIC-HR trial, viral RNA rebound was reported in 6.97% of participants who received nirmatrelvir/ritonavir and 4.10% among participants who received placebo.[79] No severe symptoms or hospitalizations were associated with the rebound. The rebound was not apparently related to viral resistance mutations or drug concentrations. Rebound viral RNA levels suggest a need for extended isolation (starting from the time of positive antigen test or return of COVID-19 symptoms) for infection control but do not change the value of this agent in reducing hospitalization for higher-risk individuals diagnosed with COVID-19. Although it's not clear that a longer course of treatment would reduce the risk of rebound, the current treatment duration is limited by the FDA EUA.

Based on EPIC-HR results, the FDA issued an EUA for Paxlovid on December 22, 2021 (most recent update July 6, 2022), 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 CYP3A4; evaluate for drug-drug interactions before administering this medication.

Tacrolimus drug-drug interaction: The drug-drug interaction with tacrolimus can lead to a rapid increase in tacrolimus concentrations to a toxic level. This can occur even with dose reduction of the nirmatrelvir/ritonavir (e.g. daily dosing) or discontinuation of tacrolimus on the day of initiation of nirmatrelvir/ritonavir. This complication of management has been reported in several case reports and has been observed in JHH transplant patients.[80]

Use is *not recommended* in patients taking tacrolimus or other calcineurin inhibitors, even these drugs are held during antiviral use. Alternative COVID treatments, such as RDV, should be pursued, if feasible. Clinicians who decide to administer nirmatrelvir/RTV to patients who are taking tacrolimus of other calcineurin inhibitors should consult with a clinical pharmacist who can assist with preemptive dose adjustments, especially for patients taking concomitant cyclosporine, sirolimus, or everolimus.

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

- Are ≥12 years old and weigh ≥40 kg
- Have mild to moderate COVID-19, without need for supplemental oxygen due to COVID-19 disease
- Are at high risk for progression to severe COVID-19, hospitalization, or death (CDC criteria):
  - BMI ≥30 kg/m^2
  - CKD (eGFR <60 mL/min/1.73 m^2)
  - 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 and genetic or metabolic syndromes

- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive-pressure ventilation requirement not related to COVID-19)

Prioritization: If a resource is limited, 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 > Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 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/1.73 m^2): 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/1.73 m^2): Paxlovid is not recommended, due to lack of data regarding dosing.
- Patients with severe hepatic impairment (Child-Pugh Class C): Paxlovid is not recommended.

Drug-drug interactions: Ritonavir is a potent inhibitor of CYP3A4; 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 Paxlovid 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, nonhospitalized adults (≥18 years old) with ≤5 days of symptoms were randomized to receive either molnupiravir 800 mg twice daily or placebo for 5 days.[81] 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 and 68 (9.7%) of placebo arm participants were hospitalized or died (RR, 31%; 95% 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 (updated March 23, 2022), 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:

- Are ≥18 years old and weigh ≥40 kg
- Have mild to moderate COVID-19, without need for supplemental oxygen due to COVID-19 disease
- Are at high risk for progression to severe COVID-19, hospitalization, or death (CDC criteria):
  - BMI ≥30 kg/m^2
  - CKD (eGFR <60 mL/min/1.73 m^2)
  - 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 and 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 > Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 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.

B. Antibody Mediation or Neutralization

Theoretically, mAbs and convalescent plasma will neutralize SARS-CoV-2 before a patient develops high neutralizing antibody titers due to the infection.

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. However, as of December 2022, mAbs previously authorized for use are no longer options for treatment of COVID-19 because they do not neutralize currently predominant circulating strains of SARS-CoV-2.

☐ Combination Antiviral Therapy

Although this writing group is not recommending routine combination antiviral therapy, it is a promising approach that may have the greatest benefit for patients who are immunocompromised or at high risk for severe COVID-19 disease. In a mouse study that used a lethal COVID-19 model, survival was improved in the nirmatrelvir plus molnupiravir arm as compared to either of those agents alone or in combination with RDV.[67] In vitro studies have also found synergy between nirmatrelvir and molnupiravir.[68]

☐ 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.[82-86] 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.[86] To be most effective, convalescent plasma should be administered as soon after infection as possible.

RCTs of convalescent plasma:

- Early RCTs of convalescent plasma treatment, which enrolled participants ≥1week after symptom onset when many had already developed neutralizing antibodies, failed to show a benefit.[87-92]

- A 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.[93] 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.[94] 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.
- An RCT with 1,181 ambulatory participants ≥18 years old, recruited regardless of comorbidities or vaccination status (17% were partially or completely vaccinated), compared 28-day hospitalization rates among those who received high-titer convalescent plasma or control plasma.[95] In the prespecified modified intention-to-treat analysis that included only transfused participants, 2.9% of convalescent plasma recipients and 6.3% of control plasma recipients were hospitalized, corresponding to a relative risk reduction of 54% (53 of the 54 hospitalized participants were unvaccinated). In subgroup analysis, participants who received convalescent plasma ≤5 days from symptom onset had a relative risk reduction of 80%; those who received convalescent plasma ≥6 days from symptom onset did not appear to have improved outcomes. The administration of convalescent plasma within 9 days (possibly further improved if given within 5 days) after the onset of symptoms reduced the risk of disease progression leading to hospitalization.

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.[96] 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.[96] 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% vs. 10.8%; *P*<.001).[97]

A large retrospective study from HCA Healthcare that included 4,337 participants who received convalescent plasma and 8,708 who did not reported 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.[98]

Novel variants (including Omicron) and convalescent plasma: High-titer polyclonal convalescent plasma, especially from people who have had recent COVID-19 and a history of immunization, has activity against subvariants except for those most recently emerging (for which they have not yet been tested *in vitro*).[99] There have not been clinical efficacy studies performed, though, with recent Omicron subvariants such as BQ.1 and BQ.1.1.

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 reported the highest titers with boosting after infection. The authors reported the 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 primary SARS-CoV-2 infection and donors who had received an mRNA booster dose 6 months after the primary series.[100] 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.[101]

Benefits and risks: As noted above, the benefit is most likely to be achieved with high-titer convalescent plasma administered early during initial acute infection, within 9 days of symptom onset (or more likely 3-5 days of symptom onset, based on 2 outpatient studies[93,95]).

The risks associated with the use of convalescent plasma include a very low risk of pathogen transmission (~1 in 2 million units),[86,102,103] allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.[102,103] 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%.[104] 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,[105] 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.** High-titer convalescent plasma supply is currently limited. Although use of high-titer convalescent plasma in early infection can be pursued, especially now that the EUA for bebtelovimab has been withdrawn by the FDA, it may be most appropriate for use in selected highly immunocompromised patients with prolonged viral infection or at risk for such (e.g., profound B cell deficiency states).

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.

Procuring high-titer units: JHH has high-titer plasma available for blood groups A, B, and O, although supply may be limited by availability. It 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). However, mismatched units can be administered upon release by the blood bank with a low risk for an adverse reaction if no more than 1 unit is given daily. 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.

- 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 treatment of hospitalized patients with mild COVID-19 symptoms who are at higher risk of clinical progression, and who are immunosuppressed or receiving immunosuppressive therapy. Available clinical trial data demonstrated benefit when high-titer convalescent plasma was administered within 3 to 5 days of symptom onset in elderly patients with mild or moderate COVID-19.[93,95] 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.

For some highly immunocompromised patients with a prolonged viral infection, convalescent plasma may be given in conjunction with RDV to enhance clearance and reduce the emergence of resistant variants. Infectious diseases (ID) consultation will be required to procure RDV.

☐ Bebtelovimab

EUA withdrawn: On November 30, 2022, the FDA withdrew the EUA for use of bebtelovimab in the U.S. because it is not expected to neutralize currently predominant circulating strains of SARS-CoV2 (BQ.1 and BQ.1.1). See FDA Announces Bebtelovimab is Not Currently Authorized in Any US Region.

There are no mAbs currently available and effective against current circulating SARS-CoV-2 variants.

☐ Tixagevimab/cilgavimab (Evusheld)

This agent has an EUA for use as pre-exposure prophylaxis. Emerging viral variants, including BA.4.6, BA.2.75.2, BA.5.2.6, BF.7, BQ.1, and BQ.1.1, are poorly neutralized by this combination agent; it is likely no longer effective.[106] Per the NIH COVID-19 Treatment Guidelines Panel statement on Omicron, "given the increasing prevalence of these resistant SARS-COV-2 subvariants, the decision to administer tixagevimab/ cilgavimab to a given patient should be based on the regional prevalence of the resistant subvariants, the individual patient's risks, the available resources, and logistics."

A study of IV tixagevimab 300 mg/cilgavimab 300 mg as treatment for COVID-19in hospitalized patients without end-organ failure and ≤12 days of symptoms included 1,417 participants randomized 1:1 for comparison with placebo.[107] The primary outcome of sustained clinical recovery at 90 days was reached by 89% in the treatment group and 86% in the placebo group (non-significant). Mortality was higher (12%) in the placebo group than in the treatment group (9%; p=0.0032). Overall, side effects were similar in both arms. Given these findings and the likely slower time to therapeutic antibody levels with this agent, its use should remain limited to pre-exposure prophylaxis, and it is not recommended for use in the treatment of acute COVID-19.

☐ Interferon Beta-1b

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.[108,109] 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.[110] 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.[110] 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 4: 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 SaO_2 ≥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 SaO_2 ≥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.
- **Sickle cell disease**: Discuss management with the sickle cell disease team prior to using cortico-steroids.

☑ **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.

- Tocilizumab may be preferred over baricitinib in pregnant patients based on limited data regarding the use of baricitinib in these populations. Because there are no clinical trials comparing tocilizumab to baricitinib, it is unclear if one or the other agent is superior.
- For patients who are profoundly hyperglycemic, baricitinib may be considered in place of dexamethasone for patients who otherwise meet the criteria for dexamethasone treatment.
- 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 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 (Johns Hopkins Bayview Medical Center), Bruce Ludwig (Howard County General Hospital), Amirali Nader (Suburban Hospital), and Mark Abbruzzese (Sibley Memorial Hospital).
- 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: have 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:**
  - Weight <30 kg: 12 mg/kg intravenously over 60 minutes
  - Weight ≥30kg: 8 mg/kg (max 800 mg) intravenously over 60 minutes
- **Baricitinib dosing:** 4 mg by mouth daily for a maximum of 14 days

☑ **Others:** Use of the following agents as treatment for COVID-19 is recommended only in a clinical trial, partly 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

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

regarding agents from the same class as tocilizumab, such as sarilumab (also an IL-6 receptor antagonist) 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)
- Ruxolitinib
- 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[111] 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.[111] 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.[112] 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.[113] 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.[114] Six of the trials were open-label, and one was placebo-controlled. Overall, steroids reduced mortality with an odds ratio of 0.66 (95% CI, 0.53–0.82). There was also reduced mortality with corticosteroid use by all assessed subgroups: with or without mechanical ventilation, ≤ 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.[115]

☐ 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.[116] 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.[117] 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, 1.19–5.12) in the budesonide group compared with the standard of care group (11.8 days vs. 14.7 days).

☐ Targeted Immune Modulators

RCT 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,[118] REMAP-CAP,[119] and RECOVERY[120] 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.[121] 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.[122] 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.[123]

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.[124]

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[125] or clinical progression at 14 days[126]; 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).[127]

In a press release from July 2020, 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).[128,129]

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.[130] 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.[131,132]

The REMAP-CAP study, an international adaptive clinical trial platform for testing multiple COVID-19 therapeutics, examined tocilizumab or sarilumab compared with standard care.[119] 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.[120] 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 SpO_2 <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.[133] 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).

Because of 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).[134]

Tocilizumab dose: Two studies have compared tocilizumab 8 mg/kg to 4 mg/kg. An RCT with 100 participants reported similar overall outcomes in the 2 arms.[135] A before-and-after study of treatment with tocilizumab 8 mg/kg compared with 4 mg/kg reported low rates of clinical events (2 deaths and 5 deaths, respectively), with no significant difference between arms.[136] Given the small size of these studies and the small number of clinical events, these data are not considered sufficient to justify switching to a 4 mg/kg dose.

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.[137] 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.[138] The ACTT-4 study compared the use of baricitinib with dexamethasone among individuals receiving RDV. The study was halted after enrolling 1,010 participants due to a low chance of identifying a difference between arms. Participants were receiving low-flow oxygen, high-flow oxygen, or noninvasive mechanical ventilation on enrollment; 75% received dexamethasone prior to enrollment (1 dose was allowed). Mechanical ventilation-free survival by day 29 was 87% in the baricitinib plus RDV arm and 87.6% in the dexamethasone plus RDV arm.[139]

With 21% of participants from the United States and most of the others from Latin American countries, the COV-BARRIER study randomized 1,526 hospitalized participants with elevated inflammatory markers (CRP, lactate dehydrogenase, ferritin, or D-dimer) who were not receiving mechanical ventilation and had not received immunosuppressive medications to receive baricitinib or placebo; 96% received corticosteroids and 19% received RDV.[140] 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).

The COV-BARRIER study assessed baricitinib use in the critically ill population among hospitalized patients who were receiving mechanical ventilation or ECMO and had elevated inflammatory markers.[122] In this subgroup, 101 participants were randomized to receive baricitinib 4 mg daily for up to 14 days or placebo; 96% of participants had ≥7 days of symptoms at study enrollment. The primary endpoint was 28-day mortality: 20 of 51 participants (39%) in the baricitinib group died compared with 29 of 50 participants (58%) in the placebo group (HR, 0.54; *P*=.03). The difference was maintained with 60-day mortality.

Between February and December 2021, the open-label, multi-arm RECOVERY trial randomized participants to receive baricitinib (n=4,149) or usual care (n=4,008); 96% received corticosteroids.[141] Eligibility requirements included hospitalization for COVID-19, no pregnancy, and no hemodialysis requirement. The primary endpoint of 28-day mortality was met by 12% of participants who received baricitinib and 14% who received usual care (age-adjusted rate ratio, 0.87; *P*=.0026).

The RUXCOVID trial tested the efficacy of the JAK inhibitor ruxolitinib in preventing death, the need for mechanical ventilation, or intensive care by day 29 in a placebo-controlled RCT.[142] Between May and September 2020, participants were randomized to ruxolitinib (n=287) or placebo (n=145); 58% of participants received corticosteroids and 6% received RDV. Outcomes were equivalent between arms.

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

- More clinical experience treating COVID-19 with tocilizumab than with baricitinib.
- Results of animal studies that suggest possible teratogenicity for baricitinib.
- Ruxolitinib is not recommended because of the limited data from a single negative RCT.

If dexamethasone is contraindicated because of profound hyperglycemia, baricitinib may be considered instead for patients who otherwise meet the criteria for dexamethasone treatment.

Anti-IL-1: 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,[30] anakinra has been used off-label to treating COVID-19. A retrospective cohort study from Italy reported that 3 of 29 patients (10%) who did receive anakinra died, compared with 7 of 16 patients (44%) who did not receive anakinra.[143] The SAVE non-randomized study[144] and SAVE-MORE placebo-controlled RCT tested the efficacy of anakinra for severe COVID-19. Participants were eligible for enrollment if they were hospitalized, required supplemental oxygen, and had a serum soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/mL (this is not a commercially available test). At enrollment, of the 594 patients included in the analysis, 91% had severe pneumonia, 86% were on dexamethasone and 74% received remdesivir. At day 28, 50.4% of participants in the anakinra group and 26.5% of those in the placebo group had fully recovered. The odds ratio for having a worse ordinal score at 28 days was 0.36 for anakinra versus placebo (p<0.0001), and anakinra reduced death from 6.9% to 3.2% (hazard ratio 0.45; p=0.045). The medication was well-tolerated, with neutropenia the only adverse event that occurred more commonly with anakinra treatment (3%) than with placebo (0.5%). On November 8, 2022, the FDA issued an EUA for anakinra to treat severe COVID-19 in hospitalized patients.

Among the 3 direct-acting immunomodulatory agents with RCT evidence of improved outcomes and FDA approval or EUA, the largest reduction in mortality has been reported with anakinra (anakinra hazard ratio 0.45; tocilizumab 0.78-0.89; baricitinib 0.65). However, the lack of head-to-head trials with other immune modulators and population differences between studies makes it impossible to rank the relative efficacy of tocilizumab, baricitinib, and anakinra.

GM-CSF inhibitors: Lenzilumab neutralizes human GM-CSF, which is a cytokine upstream from IL-6. In vitro data suggest it may limit CRS.[145] The LIVE-AIR study compared lenzilumab with placebo among 520 participants, of whom 93% received corticosteroids and 72% received RDV.[123] 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.

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.[146]

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.[147] 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.[148] When used in an animal model of influenza, BTK inhibitors rescued mice from lethal lung injury.[149] 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.[150] A case series of 19 patients with COVID-19 treated with acalabrutinib suggested overall safety and reduced inflammatory markers.[151]

☐ Other Immune Modulators

Sabizabulin: This microtubule disruptor crosslinks the α- and β- tubulin subunits to inhibit polymerization. Microtubules are intracellular transport structures critical for coronavirus cellular entry and the development of ARDS (whether a possible benefit is from an antiviral or anti-inflammatory effect is unknown). A double-blind RCT randomized 134 hospitalized participants randomized to receive sabizabulin and 70 to receive placebo. Eligibility was limited to participants who required supplemental oxygen by nasal cannula, high-flow oxygen, or mechanical ventilation and were ≥65 years old or were at risk for severe COVID-19.[152] 95% were receiving oxygen by nasal cannula or high-flow delivery. Day 60 mortality occurred in 20% (19 of 94) among the treatment arm and 45% (23 of 51) in the placebo arm (there was a 24.9% absolute risk reduction and a 55.2% relative risk reduction for death in sabizabulin recipients as compared to placebo recipients, and the odds ratio for survival in the sabizabulin arm as compared to placebo arm was 3.23 [95% CI 1.45 to 7.22; p=0.0042). Side effects were similar in both arms. After a planned interim analysis of the first 150 participants, the study was unanimously halted by an independent Data Monitoring Committee for strong evidence of efficacy. However, this agent is not currently FDA-approved for any indication. Citing the need for larger studies, an FDA advisory committee recently voted 8-5 against approving the drug for EUA status.[153]

☐ Intravenous Immune Globulin

IVIG (nonconvalescent) modulates immune response by interacting with antibodies and complementing and blocking immune cells' receptors.[154] IVIG has been used to treat multiple conditions, including SARS and COVID-19, to control pathogenic inflammation.[155] A case series of 3 patients reported using IVIG at the point of clinical deterioration and presumed shift to cytokine dysregulation.[156] 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 using mAbs (e.g., bebtelovimab) 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.[157]

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.[158] 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.[159] A review surveying 12 case reports and published studies of RDV use in pregnant and lactating patients did not reveal serious safety signals.[160]

Nirmatrelvir/ritonavir (Paxlovid): Limited animal data suggest possible reduced fetal body weight. No other adverse fetal developmental outcomes were observed. There are limited retrospective data from use in humans during pregnancy. Results of a retrospective cohort study of 47 women, mostly in the third trimester when receiving nirmatrelvir/ritonavir Paxlovid, suggested tolerability and no adverse pregnancy outcomes.[161] 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.[162,163] 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.[164] 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.[165] Four pregnant women with refractory rheumatoid arthritis appeared to benefit without adverse outcomes.[166]

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.[167] 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.[168] 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.[169] Tofacitinib use in pregnancy is described among 60 patients without notable adverse outcomes compared with background rates.[170] (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."[171] Because use of selective serotonin reuptake inhibitors 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 5: Recommendations for Agents to Avoid as Treatment for COVID-19 Specifically

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

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), either initiation or discontinuation of use
- Aspirin
- Azithromycin
- Baloxavir marboxil
- Colchicine
- Darunavir/ritonavir
- DAS 181
- Famotidine
- Favipiravir (not FDA-approved or available in the United States)
- Fluvoxamine
- Hydroxychloroquine (HCQ)*
- Indomethacin or other nonsteroidal anti-inflammatory drugs (NSAIDs)
- Ivermectin
- Lopinavir/ritonavir
- Nitazoxanide
- Oseltamivir
- Ribavirin
- Umifenovir (not FDA-approved or available in the United States)
- Vitamin C
- Vitamin D
- Zinc

*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.[172] ACE inhibitors block the ACE1 receptor but not the ACE2 receptor. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression,[173] 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.[174] The best evidence suggests similar or improved outcomes among people on chronic ACE or ARB therapy who develop COVID-19.[175]

There is no need to discontinue ACE inhibitor or ARB therapy in patients diagnosed with COVID-19; 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.[176] 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.[177] 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.[178] No clinical efficacy was found in a study of azithromycin against MERS-CoV.[179]

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 because of 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 O_2 discontinuation) compared with placebo (6.5 days).[180] 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.[181]

Darunavir/ritonavir (DRV/RTV): An in vitro study of DRV/RTV and RDV against SARS-CoV-2 reported no activity for DRV/RTV compared with potent activity for RDV.[182] Given the similar mechanism of action of DRV and LPV (see below), it is unlikely that DRV would provide benefit if LPV does not.[182]

DAS181: 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.[183] There are anecdotal reports of DAS181 use in nonresearch 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.[184] 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.[185]

Favipiravir: This inhibitor of RNA-dependent RNA polymerase has been used in China to treat patients with COVID-19.[186,187] 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.[186] 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.[187] This drug is not approved by the FDA and is not available in the United States.

Fluvoxamine: 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).[188] The primary endpoint was clinical deterioration. Clinical deterioration occurred in none of the participants in the fluvoxamine arm and 6 (8.3%) 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.[189] At 28 days, ED visit (of greater than 6 hours duration) or hospitalization occurred in 77 participants (10.4%) in the fluvoxamine arm and 108 participants (14.7%) in the placebo arm, a statistically significant finding by Bayesian analysis. Another randomized, controlled trial enrolled nonhospitalized participants to compare fluvoxamine, ivermectin, and metformin alone, combined, and with placebo in a 2 x 3 factorial design.[190] None of the 3 medications, alone or combined, prevented the primary composite endpoint of any hypoxemia, an emergency department visit, hospitalization, or death.

Another outpatient study, ACTIV-6, compared fluvoxamine 50 mg twice daily for 10 days to placebo among individuals with mild to moderate COVID-19 (no requirement for supplemental oxygen).[191] Among the 1,288 participants completing the trial, the median time from symptom onset to study drug was 5 days and 30% were unvaccinated. The time to sustained recovery (12 and 13 days) and the proportion with hospitalization, urgent care visit, or death was similar across arms (3.9% and 3.8%). This study casts further doubts on the effectiveness of fluvoxamine to improve COVID-19 outcomes.

HCQ: HCQ's in vitro activity against SARS-CoV-2 and some other viruses[192,193] 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.[194,195] Multiple RCTs, including those sponsored by the NIH, have been halted because of the futility of HCQ treatment or under-enrollment.[196-199]

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.[200]

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.[201] 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 Respiratory Medicine* 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.[202] 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.[203] Several retrospective cohort studies have compared outcomes of patients who received ivermectin with outcomes of those who did not, with mixed results regarding ivermectin's effect on outcomes.[204-208] 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) and those who received placebo.[209] 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.[210] A study conducted in Iraq among 118 participants with mild to severe COVID-19 compared 2 or 3 days of ivermectin plus doxycycline with standard therapy.[208] The time to recovery was 10.6 days in the ivermectin arm and 17.9 days in the standard therapy arm (P<.05). A (nonrandomized) 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.[210] There was no difference in symptom resolution between study arms. A living Cochrane systematic review recently concluded that there is currently low to high certainty evidence that ivermectin has no beneficial effect in outpatients or inpatients with COVID-19.[211] A study of nonhospitalized participants taking ivermectin in 1 arm of the ACTIV-6 trial employed telemedicine and home delivery of the study drug.[212] Among 1,591 participants who completed the trial, the primary endpoint of time to recovery showed a hazard ratio (HR) of 1.07 (95% credible interval [CrI], 0.96-1.17; posterior P value [HR >1] = .91). Though the drug

was administered later in the disease course (a median of 6 days from the onset of illness), this study provides more evidence against use of this antiparasitic drug in treating COVID-19.

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).[213] Another RCT of 120 patients in China suggested that LPV/RTV treatment ≤10 days from symptom onset reduced the duration of viral shedding.[214] A nonrandomized 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.[215] 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.[216] 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 with 3,424 patients who received usual care.[217]

Nitazoxanide: This agent has been tested in vitro against MERS-CoV and SARS-CoV-2 and found to have activity.[218] 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.[219]

RBV: In a systematic review, RBV was not found to be beneficial against SARS-CoV-1.[220] In a multicenter observational study of RBV plus IFN-alpha against MERS-CoV, this combination was not found to reduce mortality.[221]

Umifenovir: This agent was routinely used in China to treat patients with COVID-19.[222] 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.[223] 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.[224] 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.[225] Vitamin D was dosed as 0.532 mg calcifediol (a D_3 analog) on day 1, then 0.266 mg on days 3 and 7 and then weekly until discharge. Intensive care was required for 13 participants (50%) in the standard care group and 1 participant (2%) in the vitamin D group ($P<.001$). These 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.[226] 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.[227]

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 6: COVID-19 Pharmacologic Treatment Guidance Writing Group

- **Chair:** Paul G. Auwaerter, MD, MBA, Clinical Director, Division of Infectious Diseases; Professor of Medicine
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  - 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, RCTs. 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 are evolving rapidly, the writing group is committed to updating guidance regularly as new evidence or experience is available. The writing group recognizes the controversial nature of providing advice that draws upon minimal data. Opinions do range from providing drugs only within the context of a therapeutic trial to providing drugs with theoretical but possible benefit if risks of adverse reactions are deemed acceptable.
- Infectious diseases consultation for specific patients at high risk is advised. The writing group recommends that prescribing clinicians consult with infectious diseases clinicians for treatment of any recipient of or candidate for solid organ or bone marrow transplant. Consultation with infectious diseases clinicians for evaluation or management of any hospitalized patient with suspected (person under investigation [PUI]) or confirmed COVID-19 is otherwise up to the judgment and needs of the primary care team.

Ongoing updates: New information and experience are reviewed regularly, and the guidance is updated as needed. The JHHS community should feel free to provide comments to C19Workgrp@jhu.edu.

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Appendix A: Comparison of Selected Studies of Targeted Immunosuppression

Table A: 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) vs. PBO (n=761)	BARI 4 mg/day + RDV (n=515) vs. PBO + RDV (n=518)	Lenzilumab 1,800 mg/day (n=261) vs. PBO (n=259)	TOCI (n=249) vs. PBO (n=128)	TOCI (n=353), SARI (n=48), SOC (n=402)	TOCI (n=2,022) vs. SOC (n=2,094)
Number: Population	1,525: hospitalized; no ICU; receiving SOC	1,033: hospitalized; COVID-19 pneumonia, any	520: hospitalized; with O_2 need; no IMV	389: hospitalized; COVID-19 pneumonia; no NIV or MV	803 hospitalized w/in 24 hours of ICU organ support (high-flow O_2, MV)	4,116: hospitalized; hypoxia and CRP ≥75 mg/L
COVID-19 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 vs. 31% PBO (OR, 0.85; 95% CI 0.67–1.08)	Time to recovery: 7 days BARI/RDV vs. 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 vs. 19% PBO (HR, 0.56; 95% CI, 0.33–0.97)	Organ support–free days (median): 10 days TOCI vs. 11 days SARI vs. 0 days SOC (OR, 1.64; 95% CI, 1.25–2.14)	28-day mortality: 31% TOCI vs. 35% SOC (RR, 0.85; 95% CI, 0.76–0.94)
Secondary outcome	38% reduction in 28-day all-cause mortality: 8% BARI vs. 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 vs. 22% SARI vs. 36% control	28-day hospital discharge: 57% TOCI vs. 50% SOC (RR, 1.22; 95% CI, 1.12–1.33)
Comments	Did not meet primary endpoint	• Time to recovery with high-flow O_2 or NIV: 10 days BARI/RDV vs. 18 days PBO/RDV (RR, 1.51; 95% CI, 1.10–2.08) • 28-day mortality: 5% BARI/RDV vs. 8% PBO/RDV (HR, 0.65; 95% CI, 0.39–1.09)	92% SWOV reduction with CS + RDV (HR, 1.92; 95% CI, 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

		• SAE: 16% BARI/RDV vs. 21% PBO/RDV							

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; O_2, 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.

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Appendix B: Paxlovid Formulary Addition Memorandum

1/11/2023

MEMORANDUM

January 11, 2023

To: Nursing, Pharmacy and Prescriber Staff

From: Johns Hopkins Health System Formulary Management and Medication-Use Policy Committee

Re: Paxlovid Formulary Addition

Dear Colleagues,

On November 30th, 2022, the FDA revoked the emergency use authorization (EUA) for bebtelovimab. As a result of that decision, Paxlovid (nirmatrelvir/ritonavir) was added to the JHHS Formulary. Hospitalized patients with symptomatic mild-to-moderate COVID-19, who were not hospitalized due to COVID-19, and who are at risk for progression to severe disease may now be treated with either a 3-day course of IV remdesivir (anticipating they will be hospitalized for at least three days) or with a 5-day course of oral Paxlovid (nirmatrelvir/ritonavir).

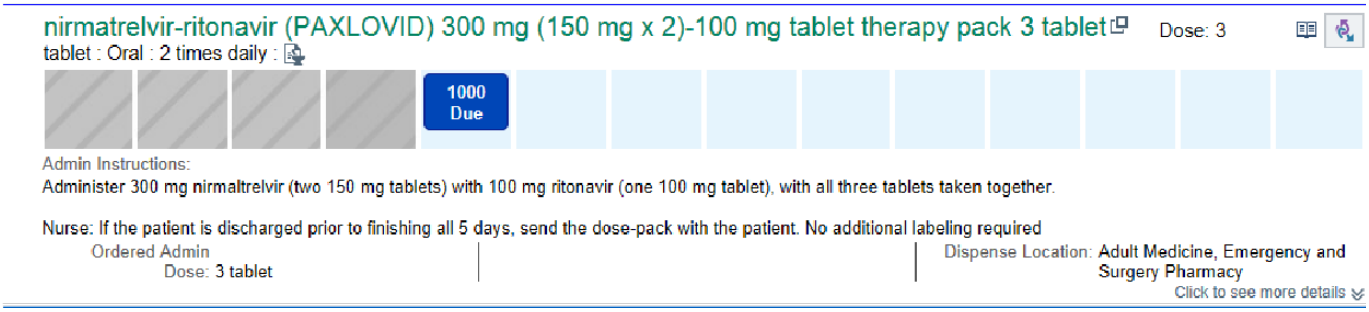
Paxlovid (nirmatrelvir/ritonavir) is only available as a 5-day dose-pack for oral administration. Therefore, we need to ensure that patients who only receive a partial course of Paxlovid (nirmatrelvir/ritonavir) during their hospitalization leave with the remaining doses in their pack to complete the course. The process outlined below should be followed to ensure safe transitions for patients as they are discharged.

JHMI Clinical Guidance for Pharmacologic Therapies for patients with mild-moderate symptomatic COVID-19 who were not hospitalized due to COVID-19	**Remdesivir 3-day course OR Nirmatrelvir/ritonavir (Paxlovid):** • Not hospitalized due to COVID-19, but at risk for progression to severe disease • Ineligible if O2 required for COVID-19 **Remdesivir 3-day course:** • ≤ 7 days new symptoms consistent with COVID-19 (fever, chills, dyspnea, cough, pharyngitis, myalgia, diarrhea, vomiting, or dysgeusia or anosmia), or at risk for severe COVID-19 • Patients warranting treatment but with contraindications to Paxlovid (e.g., drug interactions, such as the concomitant use of tacrolimus or other calcineurin inhibitors for which holding these are insufficient to mitigate risk with Paxlovid) **Nirmatrelvir/ritonavir (Paxlovid)** • ≤5 days of new symptoms consistent with COVID-19 (fever, chills, dyspnea, cough, pharyngitis, myalgia, diarrhea, vomiting, or dysgeusia or anosmia) and ≥12 years old • Preferred if the patient is not expected to be hospitalized for ≥ 3 days and has no contraindications to Paxlovid

	- Significant Drug-Drug interactions will flag in Epic. Please see the DDI table in the JHMI Clinical Guidelines for more detail. • Must meet EUA criteria for Paxlovid For comprehensive guidance, please see the JHMI Clinical Guidance for Pharmacologic Therapies Guidelines.
Nursing Discharge Process	If the patient is being discharged prior to completing their course of Paxlovid: • Ensure that the patient is given the remaining dose pack to take home with them to finish the course of therapy. • The dose pack will be labeled appropriately for outpatient use; no modifications/additional labeling is required prior to discharge.
Provider Discharge Process	For patients who are being discharged prior to completing their course of inpatient therapy with Paxlovid: • **Do <u>not</u> send a new prescription** for Paxlovid to the outpatient pharmacy. Continue the inpatient order at discharge. This will allow Paxlovid to be included in the discharge medication list and the AVS. Ensure that the remaining number of days of therapy is accurate on the AVS. • The patient will be discharged with the remaining dose pack that they started inpatient. This package will be labeled appropriately for outpatient. For patients who are being discharged from the emergency department • Continue to send outpatient prescriptions

Please contact the Drug Information Service via email for questions regarding this information.

Paxlovid MAR Screenshot:



Appendix C: Non-Oncology Remdesivir Referral Workflow

1/26/2023

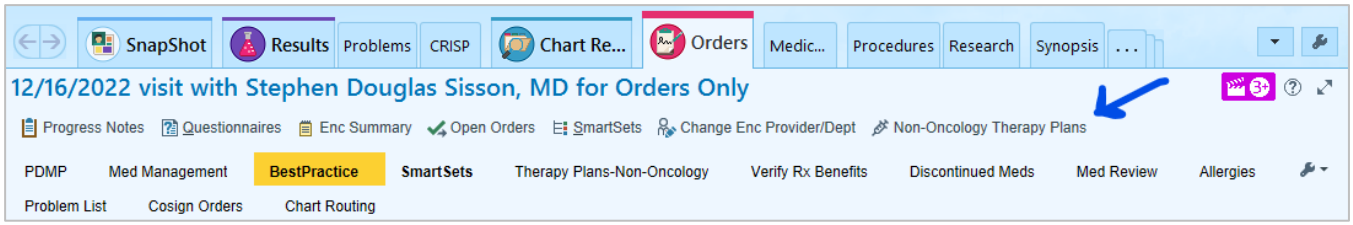
Introduction

- For all patients, Paxlovid is the preferred first-line antiviral treatment for COVID-19. Workflows herein are for patients who have a medical contraindication to Paxlovid.
- JHM Oncology patients have a separate workflow specific to Oncology.
- For all patients who cannot tolerate Paxlovid, the best first option is to refer the patient to the Baltimore Convention Center Field Hospital (referral form **here**).
- For patients who cannot tolerate Paxlovid **and** for whom there is no capacity at the Baltimore Convention Center Field Hospital **and** are within 7 days of the onset of symptoms **and** are at **risk** for progression to severe disease, prescribe remdesivir.
  - Remdesivir is a 3-day infusion ordered through a *non-oncology therapy plan*.
  - **Remdesivir is contraindicated in patients liver enzymes (AST/ALT/Alkaline Phosphatase) greater than ten times the upper limit of normal.**
  - The FDA warns of use of remdesivir for patients with GFR<30ml/min. JHM experience is that remdesivir is safe in CKD, including those on dialysis. A conversation of the risks/benefits of remdesivir with such patients should be documented in the therapy plan.
- On weekdays, remdesivir infusion shall be provided at the Park Infusion Center on the East Baltimore campus. On weekends and holidays, remdesivir infusion shall be provided in the Oncology urgent care center in Weinberg.

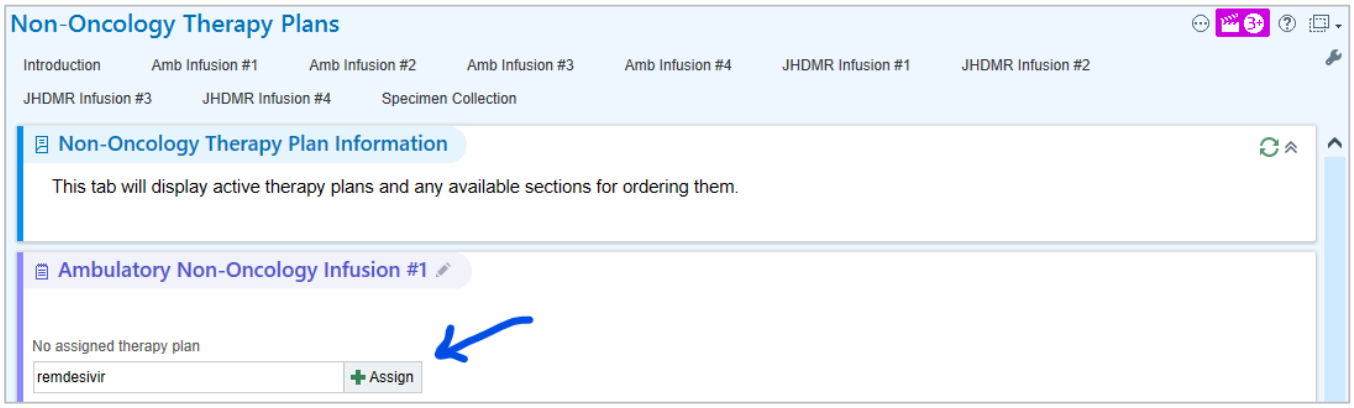
Ordering Instructions

Weekday start: Non-oncology patients who need remdesivir infusion for COVID-19 and who will be starting the three-day infusion plan on a weekday shall be infused at the Park Infusion Center on the JHH Campus. If the three-day span of treatment includes weekend days, weekend day infusions shall be done in the Weinberg Oncology Urgent Care treatment site.

1. For the affected patient, open an encounter and under the Orders tab, select 'Non-Oncology Therapy Plans.'



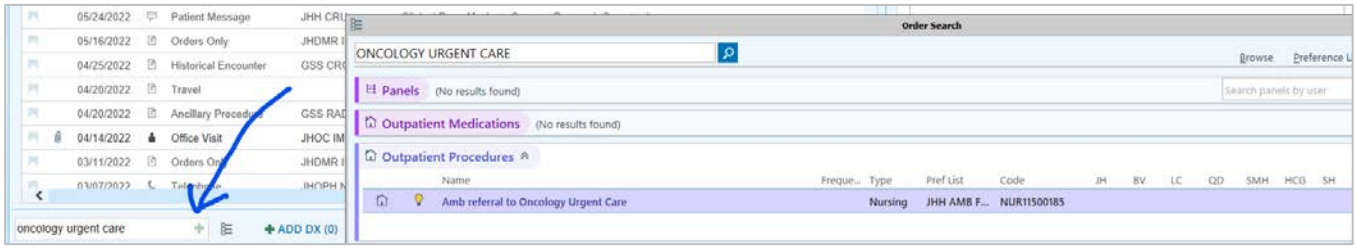
2. In the Ambulatory Non-Oncology Infusion #1 plan, enter 'remdesivir' and click 'Assign'. Note the therapy plan includes orders to check a comprehensive metabolic panel. **Remdesivir is contraindicated in patients with liver enzymes greater than 10X the upper limit of normal**. Conversation with the patient of risks/benefits of remdesivir in patients with CKD should be documented in the therapy plan.



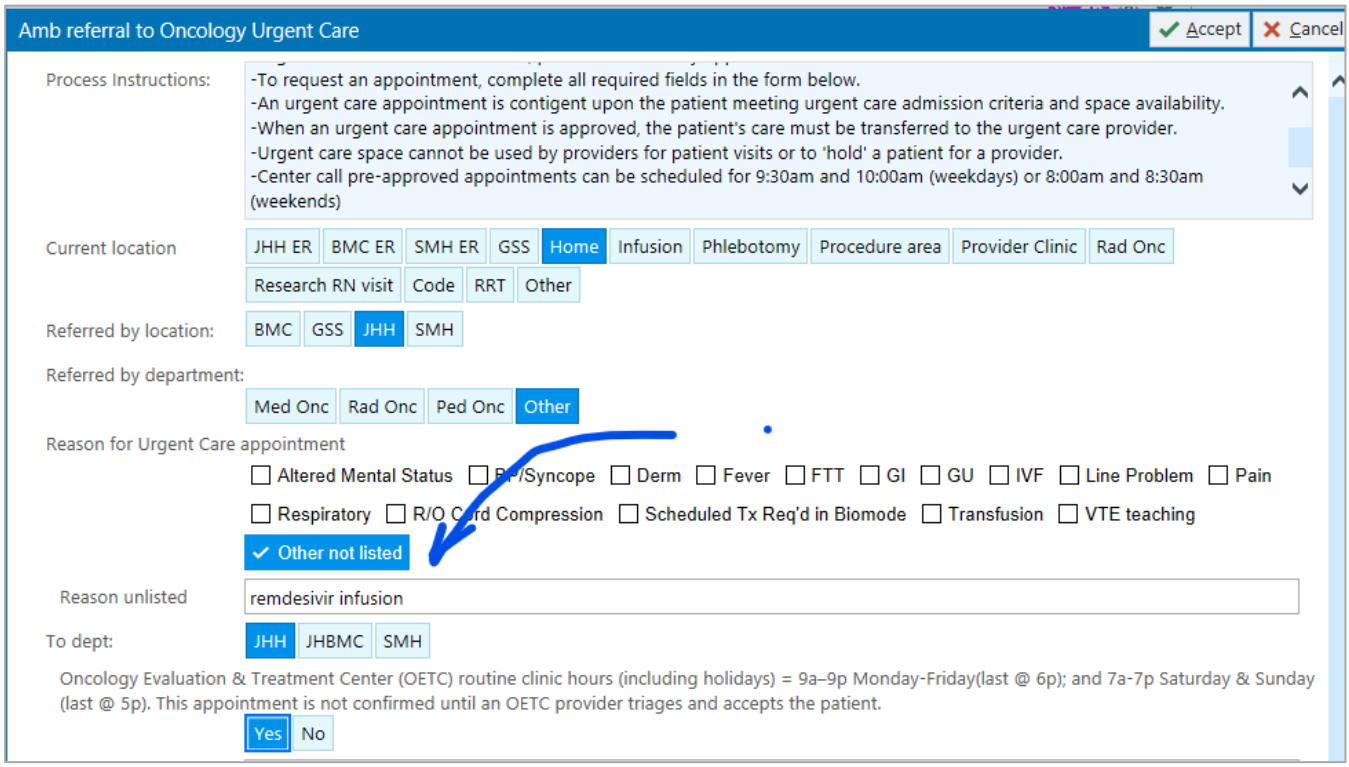
3. Once the therapy plan is submitted, send a simultaneous email to adultivinfusion@jhmi.edu to alert them to the patient. The Park Infusion team will reach out to the patient to schedule and provide instructions to the patient.
4. On day 1 of infusion, the infusion team will send a comprehensive metabolic panel as part of the therapy plan. *It is your responsibility to review those results, which will likely finalize after day 1 of infusion is complete.* If liver enzymes are greater than 10X the upper limit of normal:
   a. Notify the patient that no further infusions shall be administered and cancel the remainder of the therapy plan.
   b. Notify the Park Infusion team through email at adultivinfusion@jhmi.edu .
   c. If the patient is getting infusion in Oncology, send a secure chat message to JHH Oncology Urgent Care All Combined Group to notify them of the change.
5. If the 3-day infusion course includes a weekend or holiday, you will need to refer the patient to Oncology Urgent Care as described below. Oncology will assume care of the referred patient on weekends and holidays.

Weekend/holiday start: Non-oncology patients who need remdesivir infusion that starts on a weekend or holiday shall start treatment at the Oncology Urgent Care clinic in Weinberg. Infusion shall typically be completed in Park Infusion; therefore, referral to Oncology Urgent Care **and** a non-oncology therapy plan for remdesivir must be ordered at the same time, as follows:

1. To refer a patient who needs to start remdesivir infusion on a weekend or holiday, open an Epic encounter and search for 'oncology urgent care' in the order box.



2. Complete the referral form, with 'Reason for Urgent Care appointment' as 'Other not listed', noting referral is for remdesivir infusion. The Oncology team will reach out to the patient during clinic hours (9AM – 9PM M-F; 7AM – 7PM Saturday/Sunday/holidays).



3. In most cases (other than 3-day weekends due to holiday) the 3-day infusion shall be completed at Park Infusion. After placing the referral to Oncology Urgent Care, complete an order for Remdesivir infusion as outlined in the 'Weekday start' section above. **You must complete a non-oncology therapy plan for the doses of remdesivir that are to be administered in Park Infusion.** The Oncology team will instruct the patient on their appointment at Park Infusion. You will assume responsibility for the clinical care of the patient getting remdesivir infusion at Park.