JHMI Clinical Recommendations for Pharmacologic Treatment of COVID-19 in Adults

Source: JHU COVID-19 Treatment Guidance Writing Group; JHH COVID-19 Treatment Guidance Working Group

Date: August 31, 2023, v2; replaces the last update of January 20, 2023

New in This Update: September 1, 2023

- Revised format focusing on preferred and alternative pharmacologic agents for treating COVID-19 in adults at risk of or with severe disease. See: Recommendations | Summary tables | Discussion of key clinical trials
- Recommendations for treatment of protracted COVID-19 in severely immunocompromised adults.
- Although available through an Emergency Use Authorization (EUA) of the U.S. Food and Drug Administration (FDA), this writing group recommends against using vilobelimab for COVID-19 treatment.

Contents

I. Purpose of This Guideline

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 hospitalized and ambulatory patients diagnosed with SARS 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.

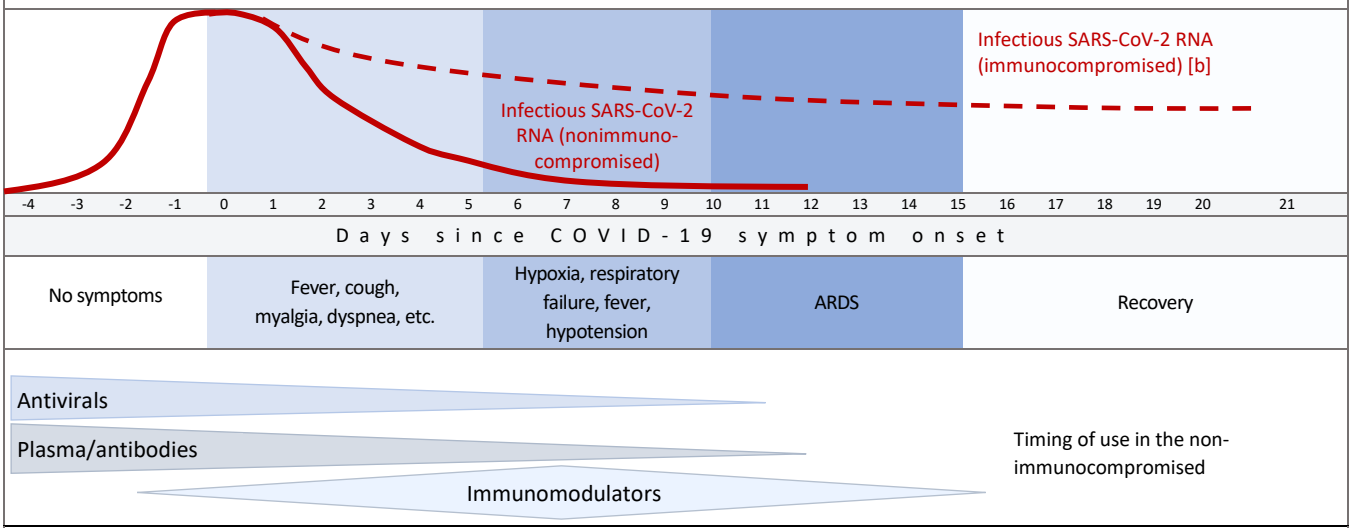
A. Approaches to Treatment

COVID-19 disease ranges from mild, with upper respiratory symptoms, to acute and life-threatening pneumonia and systemic disease. It can progress to a protracted viral infection with associated morbidity among highly immunocompromised patients. Following recovery from the acute or prolonged viral infection, post-COVID-19 sequelae can persist for weeks, months, or years. Antiviral agents, convalescent COVID-19 plasma, and immunomodulatory therapies can change the course of the disease by reducing severity, including lowering mortality.

Approach: Approaches to 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]).

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), common symptoms, and possible timing of therapeutics for the most significant benefit. Symptoms and viral shedding may be prolonged in some substantially immunocompromised patients. 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 more extended period of infectious virus, i.e., >10 days in normal hosts.[1-7]

b. In immunocompromised individuals, duration is variable, especially severely immunocompromised (longer).

B. Clinical Considerations

The primary factors that require consideration in the management of COVID-19 disease include:

Symptoms: Does the patient have mild or severe symptoms as defined by a supplemental oxygen requirement?

Risk for severe disease: Is the patient at increased risk of severe COVID-19 due to age >65 years (the strongest risk factor) or chronic comorbidities such as cardiovascular disease and diabetes, pregnancy, or immunosuppression (see Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals).

Immune status: Is the patient relatively immunocompetent, or is the patient highly immunosuppressed (especially with compromised B-cell activity or solid organ transplantation)? Has the patient had an adequate antibody response to vaccination?

Vaccination status: Has the patient been vaccinated or had prior SARS-CoV-2 infection? Does an impaired immune status compromise the patient's response to vaccination?

Treatment setting: Is treatment occurring in a hospital setting with ease of access to infusion and monitoring or an outpatient setting with different medication access?

Pregnancy: Data are insufficient to evaluate a drug-associated risk of major congenital disabilities, miscarriage, or adverse maternal or fetal outcomes using currently available COVID-19 therapeutics. Remdesivir (RDV) is being used routinely during pregnancy for those who are hospitalized, as are protease inhibitors for oral therapy (nirmatrelvir/ritonavir) without any notable teratogenicity and as suggested by the American College of Obstetricians and Gynecologists after discussion of risks/benefits with the patient (see ACOG: COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics). Baricitinib and molnupiravir should be avoided during pregnancy. Other 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.

C. Treatment of Immunocompromised Patients With Protracted COVID-19

Among patients who have received solid organ or hematopoietic cell transplantation, have a hematologic malignancy (leukemia, lymphoma, myeloma), received chimeric antigen receptor therapy (CAR-T), or are otherwise severely B-cell depleted, SARS-CoV-2 replication may persist for weeks or months and contribute to morbidity and mortality.[1,2,8-12] "Protracted COVID-19" refers to SARS-CoV-2 replication and disease persisting >21 days and is characterized by signs or symptoms of ongoing COVID-19 along with a lower cycle threshold (Ct) value for SARS-CoV-2 rtPCR.[9,13,14] Lower Ct values offer supportive evidence of ongoing SARS-CoV-2 replication causing disease (e.g., Ct ≤30 cycles), although Ct values lack standardization or validation.[9,14] Persistent viral positivity between days 10 to 21 fits into managing acute COVID-19 in highly immunocompromised individuals.

Therapies: Options for avoiding protracted SARS-CoV-2 infection in this patient population include using RDV for 10 days in those who cannot take a protease inhibitor. For patients with protracted COVID-19, combination antiviral therapy is preferred based on favorable outcomes reported in case series and the experience at JHH. Case reports and case series have described the use of RDV plus convalescent plasma and convalescent plasma alone. Combination antiviral therapy with nirmatrelvir/ritonavir (RTV) and RDV and molnupiravir and RDV has also been used with favorable outcomes reported in case series, sometimes with courses longer than the recommended 5-day course of nirmatrelvir/RTV or molnupiravir.[15-21]

II. JHMI Clinical Recommendations for Pharmacologic Treatment of COVID-19 in Adults

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

General principles:

- Treat adult patients at risk of progression to severe COVID-19 within 5 to 7 days of symptom onset with a preferred or alternative antiviral agent (see below) based on the treatment setting and clinical considerations.
- Treat adult patients with severe COVID-19 disease (SaO_2<94%) within 10 days of symptom onset with RDV based on clinical considerations.
- Use dexamethasone in patients with a room air SaO_2 <94%. (Consult with the JHMI sickle cell team before initiating corticosteroids in a patient with sickle cell disease.)
- Add tocilizumab to antiviral therapy and dexamethasone in patients with clinical progression (see below) after dexamethasone initiation.

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

Immunosuppressed patients:

- Consult with the transplant and oncology infectious diseases regarding clinical decision-making for highly immunosuppressed patients.
- Recommend concomitant treatment with RDV and convalescent plasma for severely immunocompromised patients.

Immunosuppressed patients with protracted SARS-CoV-2 infection:

- **Inpatient:** For highly immunosuppressed patients, use combination therapy regardless of prior treatment. Use convalescent high-titer COVID plasma (2 to 3 units) plus RDV for 10 days plus either nirmatrelvir/RTV for 5 days or molnupiravir for 5 days. (Molnupiravir is preferred when significant drug-drug interactions exist with nirmatrelvir/RTV; however, access for hospitalized patients is limited and depends on obtaining an outpatient prescription and ordering for inpatient use with "patient-supplied medicine" order in Epic.)
  - Nirmatrelvir/RTV is *not recommended* in patients taking tacrolimus or other calcineurin inhibitors, even if these medications are held for the duration of antiviral use. Risks of calcineurin toxicity, such as posterior reversible encephalopathy syndrome (PRES), may still occur.
- **Outpatient**: Use combination therapy, high-titer convalescent COVID plasma (2 to 3 units), plus RDV for 5 to 10 days plus molnupiravir for 5 days.
  - Exercise caution in prescribing 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.[22]

Avoid the use of:

- **Vilodelimab:** Insufficient evidence to support routine use as a treatment for COVID-19 in any population; the pivotal trial on which the FDA based its EUA included a substantial number of participants also receiving tocilizumab. [a]
- **Metformin**: Currently available evidence does not support the use of metformin to prevent post-COVID-19 syndromes or acute management of COVID-19. [b]
- **Clinical trial data indicate no benefit or potential harm:** Azithromycin, colchicine, DAS 181, hydroxychloroquine, ivermectin, nitazoxanide, oseltamivir, vitamin D, vitamin D, and zinc.

Abbreviations: ECMO, extracorporeal membrane oxygenation; FDA EUA, U.S. Food and Drug Administration Emergency Use Authorization; G-CSF, granulocyte colony-stimulating factor; IgG, immune globulin; IL6, interleukin-6; JHMI, Johns Hopkins Medical Institutions; RCT, randomized controlled trial; RDV, remdesivir; RTV, ritonavir; SaO_2, saturation of arterial blood

Notes:

a. See clinical trials

b. See clinical trials

A. Treatment of COVID-19 in Adults at Risk for Severe Disease (Ambulatory or Inpatients Not Primarily Hospitalized for COVID-19)

Table 1: Preferred and Alternative Pharmacologic Agents for Treatment of COVID-19 in Adults at Risk for Severe Disease (Ambulatory or Inpatients Not Primarily Hospitalized for COVID-19)

Preferred Agents

Remdesivir (Veklury)

JHHS recommends the treatment of: ▪ Ambulatory patients ≤7 days of COVID-19 symptoms ▪ Hospitalized patients admitted for non-COVID-19 conditions with ≤7 days of new symptoms consistent with COVID-19 and no supplemental O_2 requirement for COVID-19. ▪ See clinical trials	**Administration and duration**: 3-day course ▪ Infusion day 1: 200 mg IV loading dose ▪ Infusion days 2 and 3: 100 mg IV	**Cautions and adverse effects:** ▪ Concomitant use with strong CYP3A4 inducers such as rifampin may reduce RDV levels. · Also see: Liverpool COVID-19 Drug Interactions Checker ▪ Discontinue and do not re-start RDV if ALT or AST levels rise to >10 times the upper limit of normal or if the patient has symptoms of drug-induced liver injury ▪ Potential for hypersensitivity, including infusion-related and anaphylactic reactions ▪ Most common adverse effects include nausea and increases in ALT and AST ▪ Rare or occasional adverse effects include hypoglycemia, insomnia, elevated prothrombin time (without a change in INR), pyrexia, rash, and elevated transaminase level	**Notes:** ▪ FDA-approved ▪ No dose adjustment is required with impaired liver or kidney function ▪ Daily AST and ALT monitoring is recommended ▪ May consider use in pregnancy **JHMI requirements:** ▪ Order through Epic; discontinue upon hospital discharge ▪ If a patient with a new COVID-19 infection develops an O_2 requirement, additional approval is required via a process determined by each hospital in the JHHS system ▪ Do not admit to the hospital or delay discharge for RDV administration · See: Referral notes for ambulatory patients

Nirmatrelvir/RTV (Paxlovid)

JHHS recommends the treatment of: ▪ Patients ≤5 days of mild-to-moderate symptoms, with no supplemental O_2 requirement ▪ Patients ≥65 years old OR with chronic comorbidities ▪ Not authorized for patients hospitalized for severe or critical COVID-19 (See Appendix A) **Not recommended for patients who:** ▪ Take tacrolimus or other calcineurin inhibitors ▪ Have severe renal impairment (eGFR <30 mL/min) ▪ Have severe hepatic impairment (Child-Pugh Class C) ▪ See clinical trials	**Administration and duration:** ▪ Nirmatrelvir 300 mg/RTV 100 mg by mouth twice daily for 5 days ▪ Not authorized for >5 days consecutive use	**Cautions and adverse effects:** ▪ Monitor for drug-drug interactions before, during, and for up to 2 weeks after the last dose of medication ▪ RTV is a potent inhibitor of CYP3A4. Consult clinical pharmacologist as needed · Also see: Liverpool COVID-19 Drug Interactions Checker ▪ Most common adverse effects include dysgeusia and diarrhea	**Notes:** ▪ FDA-approved; EUA continued ▪ Concomitant convalescent plasma therapy may be beneficial in patients with immunosuppression ▪ Pregnancy: Limited data suggest nirmatrelvir/RTV may be safe ▪ Viral rebound occurs in treated and untreated individuals with COVID-19. The rebound is usually milder than the first illness, and additional courses of treatment are not indicated **JHMI requirements:** ▪ Do not use for patients requiring oxygen for COVID-19 illness (see Appendix A) ▪ Check for drug interactions; consider using 3-day RDV in unstable patients who may require drugs that would interact. ▪ Order through Epic

Table 1: Preferred and Alternative Pharmacologic Agents for Treatment of COVID-19 in Adults at Risk for Severe Disease (Ambulatory or Inpatients Not Primarily Hospitalized for COVID-19)

Alternative Agent			
Molnupiravir (Lagevrio)			
JHHS recommends the treatment of: ▪ Patients with ≤5 days of non-severe, non-critical COVID-19 symptoms and no supplemental O_2 requirement if preferred agents are unavailable ▪ See clinical trials	**Administration and duration:** 800 mg (4 capsules, 200 mg each) by mouth every 12 hours for 5 days	**Cautions and adverse effects:** ▪ Teratogenicity and mutagenicity concerns in pregnancy ▪ Most common adverse effects include diarrhea, nausea, and dizziness ▪ FDA EUA notes no drug-drug interactions based on limited available data	**Notes:** ▪ FDA EUA authorized ▪ Alternative if preferred agents are unavailable (preferred agents have greater clinical efficacy in reducing severe COVID-19 or death) ▪ Prescribe through retail pharmacies for ambulatory patients when indicated ▪ Unavailable in the JHMI system for the treatment of hospitalized patients; it can be prescribed before the patient is admitted, and the patient's family can bring the medication, which can be dispensed using a "patient supplied medicine" order in Epic

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C-reactive protein; CYP3A4, cytochrome P450 3A4; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; FDA, U.S. Food and Drug Administration; ID, infectious diseases; INR, international normalized ratio; IV, intravenous; JHHS, Johns Hopkins Health System; JHMI, Johns Hopkins Medical Institutions; O2, oxygen; PCR, polymerase chain reaction; P&T, Pharmacy & Therapeutics Committee; RDV, remdesivir.

B. Inpatient Treatment of Adults with Severe COVID-19

Table 2: Preferred and Alternative Pharmacologic Agents for Inpatient Treatment of Severe COVID-19 in Adults

Preferred Agents			
Remdesivir (Veklury)			
JHHS recommends the treatment of: ▪ Patients hospitalized for COVID-19 treatment with ≤10 days of symptoms and supplemental O_2 requirement or ≤24 hours ECMO or mechanical ventilation duration before RDV initiation ▪ Highly immunosuppressed [a] patients: Any O_2 requirement and ICU care are allowed. RDV may be started 10 days after symptom onset ▪ See clinical trials	**Administration and duration:** ▪ **5-day IV infusion:** · Day 1: 200 mg IV loading dose · After day 1: 100 mg IV for the duration of treatment ▪ **>5 days IV infusion:** If a patient is hospitalized without invasive mechanical ventilation or ECMO and there is no improvement after a 5-day infusion, treatment may be continued for up to 10 days ▪ **>10 days IV infusion:** May be considered for highly immunosuppressed patients, including those with protracted COVID-19 [b].	**Cautions and adverse effects:** ▪ No dose adjustment is required for impaired kidney function ▪ Concomitant use with strong CYP3A4 inducers such as rifampin may reduce RDV levels. · See: Liverpool COVID-19 Drug Interactions Checker ▪ Discontinue and do not re-start RDV if ALT or AST levels rise to >10 times the upper limit of normal or if the patient has symptoms of drug-induced liver injury ▪ Potential for hypersensitivity, including infusion-related and anaphylactic reactions ▪ Most common adverse effects include nausea and increases in ALT and AST ▪ Rare or occasional adverse effects include hypoglycemia, insomnia,	**Notes:** ▪ FDA-approved ▪ Concomitant convalescent plasma therapy may be beneficial for patients with immunosuppression [a] ▪ Daily AST and ALT monitoring is recommended ▪ May consider use in pregnancy **JHMI requirements:** ▪ Order through Epic; discontinue upon hospital discharge ▪ If a patient with a new COVID-19 infection develops an O_2 requirement, additional approval is required via a process determined by each hospital in the JHMI system ▪ Do not admit to the hospital or delay discharge for RDV

Table 2: Preferred and Alternative Pharmacologic Agents for Inpatient Treatment of Severe COVID-19 in Adults			
		elevated prothrombin time (without a change in INR), pyrexia, rash, and elevated transaminase level	administration if the patient has sufficiently improved
Dexamethasone			
JHHS recommends the treatment of: ▪ Patients with supplemental O_2 requirement; ICU use is allowed ▪ See clinical trials	**Administration and duration:** ▪ 6 mg IV or oral once daily for up to 10 days or until hospital discharge	**Cautions and adverse effects:** ▪ Use in pregnant patients is the same as in the nonpregnant ▪ Before treating patients with sickle cell disease, discuss use with the JH Sickle Cell Disease team	**Note:** ▪ Can substitute another corticosteroid if dexamethasone is unavailable
Tocilizumab (Actemra)			
JHHS recommends the treatment of: ▪ Hospitalized patients receiving dexamethasone who require high-flow oxygen or are within the first 24 hours of ICU care for organ support, including mechanical ventilation. Concomitant systemic corticosteroid therapy is recommended ▪ See clinical trials	**Administration and duration:** ▪ Single IV infusion, weight <30 kg: 12 mg/kg over 60 minutes ▪ Single IV infusion, weight ≥30 kg: 8 mg/kg (max 800 mg) over 60 minutes	**Cautions and adverse effects:** ▪ Exercise caution when co-administering tocilizumab with CYP3A4 substrate drugs when a decrease in effectiveness is undesirable ▪ Most common adverse effects include constipation, anxiety, diarrhea, insomnia, hypertension, nausea	**Notes:** ▪ FDA EUA authorized ▪ May consider use in pregnancy ▪ Patients with evidence of clinical progression of COVID-19 are most likely to benefit. **JHMI requirements:** ▪ P & T chair or designee approval ▪ CRP >7.5 required for immunocompetent patients ▪ CRP is not required for immunocompromised patients
Convalescent Plasma			
JHHS recommends the treatment of: ▪ Hospitalized patients with or without O_2 requirement who are immunosuppressed [a] or receiving immunosuppressive therapy ▪ Ambulatory patients who are immunosuppressed ▪ Consider for patients with impaired humoral immunity ▪ See clinical trials	**Administration and duration:** ▪ IV infusion, initiate with 1 unit (200 mL) ▪ Additional units may be administered based on the patient's clinical response	**Cautions and adverse effects:** ▪ Limited supply of high-titer units ▪ Minimal adverse events have been reported from clinical trials, although transfusion reactions are possible	**Notes:** ▪ FDA EUA authorized ▪ For highly immunosuppressed ambulatory patients, consider concomitant nirmatrelvir/RTV; if contraindicated, consider RDV or molnupiravir ▪ Concomitant RDV may enhance viral clearance and reduce the emergence of resistant variants ▪ A high-titer is required to neutralize Omicron variants (consider ABO match) · See Procuring high-titer units. ▪ The response appears to be better early in the course of COVID-19 disease ▪ May consider using in pregnancy if identical ABO match ▪ Blood type mismatch (compatible) units are allowed, but the infusions are limited to 1 unit/per day in nonpregnant patients

Table 2: Preferred and Alternative Pharmacologic Agents for Inpatient Treatment of Severe COVID-19 in Adults

Alternative Agents

Baricitinib (Olumiant)

JHHS recommends the treatment of:	Administration and duration: 4 mg by mouth daily for 14 days (maximum)	Cautions and adverse effects:	Notes:
▪ Hospitalized patients (including ICU for ≤24 hours) with severe COVID-19 who require supplemental O_2 for COVID-19 management ▪ See clinical trials		▪ Results from animal studies raised concerns for use in pregnancy; see text ▪ Adverse events include elevation in ALT and hypersensitivity reactions	▪ FDA EUA authorized ▪ Recommended alternative agent if tocilizumab is not available or if dexamethasone is contraindicated ▪ If dexamethasone is contraindicated because of profound hyperglycemia, baricitinib may be considered instead for patients who otherwise meet the criteria for dexamethasone treatment **JHMI requirement:** ▪ P&T chair or designee approval

Anakinra (Kineret)

JHHS recommends the treatment of:	Administration and duration:	Cautions and adverse effects:	Notes:
▪ Hospitalized (including ICU ≤24 hours) patients with progressive COVID-19 disease and supplemental O_2 requirement ▪ See clinical trials	▪ 100 mg administered daily by subcutaneous injection for 10 days ▪ Dose adjustment for CrCl <30 mL/min: Consider 100 mg every other day for 5 total doses over 10 days	▪ Not recommended for use in combination with TNF-blocking agents ▪ Dose adjustment is required for patients with severe renal insufficiency or end-stage renal disease ▪ Most common adverse effects include increased transaminases, neutropenia, rash, and injection site reactions ▪ Pregnancy: Data are insufficient to rule out potential fetal harm	▪ FDA EUA authorized ▪ Use in combination with dexamethasone if tocilizumab and baricitinib are unavailable or contraindicated ▪ It may be considered if dexamethasone is contraindicated due to profound hyperglycemia **JHMI requirement:** ▪ P&T chair or designee approval is required

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C-reactive protein; CYP3A4, cytochrome P450 3A4; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; FDA, U.S. Food and Drug Administration; ICU, intensive care unit; ID, infectious diseases; INR, international normalized ratio; IV, intravenous; JHHS, Johns Hopkins Health System; JHMI, Johns Hopkins Medical Institutions; O2, oxygen; PCR, polymerase chain reaction; P&T, Pharmacy & Therapeutics Committee; RDV, remdesivir; TNF, tumor necrosis factor.

Notes:

a. Immunosuppression, 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).

b. **For highly immunosuppressed patients who have protracted COVID-19 disease, clinicians should:**
   - Consult with the transplant and oncology infectious diseases teams regarding clinical decision-making
   - Treat hospitalized patients with 2 to 3 units of convalescent plasma PLUS 10 days of RDV PLUS 5 days of nirmatrelvir/RTV OR 5 days of molnupiravir (molnupiravir is generally preferred because it has fewer drug-drug interactions than nirmatrelvir/RTV; however, access to this medication may be limited in the hospital setting)
   - Treat ambulatory patients with 2 to 3 units of convalescent plasma PLUS 10 days of RDV PLUS 5 days of molnupiravir

C. Treatment of Highly Immunosuppressed Patients with Protracted COVID-19

Consult with the transplant and oncology infectious diseases teams regarding clinical decision-making. Typical approaches considered:

Hospitalized patients: 2 to 3 units of convalescent plasma plus 10 days of RDV plus 5 days of nirmatrelvir/RTV or 5 days of molnupiravir (molnupiravir is generally preferred because it has fewer drug-drug interactions than nirmatrelvir/ RTV; however, access to this medication may be limited in the hospital setting)

Ambulatory patients: 2 to 3 units of convalescent plasma plus 10 days of RDV plus 5 days of molnupiravir

III. Summary of Key Clinical Trial Evidence for Preferred, Alternative, and Agents to Avoid

FDA-approved medications for the treatment of COVID-19 include remdesivir (Veklury), nirmatrelvir/ritonavir (Paxlovid), tocilizumab (Actemra), and baricitinib (Olumiant). Medications available through FDA EUAs include molnupiravir (Lagevrio), anakinra (Kineret), and vilobelimab (Gohibic). Dexamethasone does not have a specific FDA indication for COVID-19 but has become a standard part of treating severe COVID-19. Monoclonal antibodies are no longer available because they are not effective against strains of SARS-COV-2 that are now circulating in the United States. See: FDA > Coronavirus (COVID-19) Drugs.

Below are the currently available preferred, alternative, and not recommended agents for treating adults with COVID-19, with summaries of the key clinical trials providing evidence supporting each agent.

A. Preferred Agents

Remdesivir (Veklury; RDV)

- **ACTT-1:** This double-blind, placebo-controlled trial with sites in North America, Europe, and Asia randomized 1,062 participants with severe COVID-19 pneumonia, defined as infiltrates on imaging or oxygen saturation (SaO2) <94%, to receive 10 days of RDV or placebo. RDV was stopped for participants ready for discharge before completing 10 days of treatment. Through 28 days of observation following randomization, participants in the RDV arm had a median time to recovery of 10 days compared with 15 days among those in the placebo arm (P<.001).[23] 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.
- **SOLIDARITY:** This pragmatic, open-label RCT of RDV, hydroxychloroquine, lopinavir/ritonavir, and subcutaneous IFN beta 1a[24] 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 compared 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.
- **DisCoVeRy:** This is 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.[25] There were 429 participants in the RDV arm and 428 in the standard-of-care arm; 70% were men, 59% received oxygen via nasal cannula 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.

- **PINETREE**: This 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.[26] 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.

Nirmatrelvir/Ritonavir (Nirmatrelvir/RTV; Paxlovid)

The EPIC-HR RCT enrolled unvaccinated ambulatory adults (≥18 years old) at risk for progression to severe COVID-19 with ≤5 days of symptoms at randomization to receive nirmatrelvir/RTV or placebo. 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.

Dexamethasone (multiple trade names)

Systemic corticosteroids:

- **EPIC**: This trial enrolled unvaccinated ambulatory adults (≥18 years old) at risk for progression to severe COVID-19 with ≤5 days of symptoms at randomization to receive nirmatrelvir/RTV or placebo. 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 in the placebo arm. Adverse events were overall lower in the nirmatrelvir arm.
- **RECOVERY:** 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.[27] The 2,104 participants randomized to the dexamethasone arm received 6 mg orally 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, a common complication of viral pneumonitis/ARDS. Thus, dexamethasone is the preferred glucocorticoid for treating nonpregnant patients. As noted above, prednisolone or hydrocortisone are reasonable alternatives for pregnant patients to achieve lower fetal glucocorticoid concentrations.
- **GLUCOCOVID:** 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.[28] 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 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 with 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 requirements.

- **Study with participants ≥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 those who did not.[29] 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 the 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.[30] 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.

Inhaled corticosteroids:

- **STOIC:** This open-label RCT compared treatment with inhaled budesonide (400 µg of dry turbo inhaler powder twice daily) to the standard of care among participants with ≤7 days of mild COVID-19 symptoms.[31] The primary endpoint was any COVID-19-related urgent or emergency care visit or hospitalization. In the 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.
- **PRINCIPLE:** This open-label, adaptive RCT compared inhaled budesonide (n=787) with the 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.[32] 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).

Tocilizumab (Actemra)

Among the 3 direct-acting immunomodulatory agents with RCT, evidence of improved outcomes, and FDA approval or EUA, the most significant 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 modulator use and population differences between studies makes it impossible to rank the relative efficacy of tocilizumab, baricitinib, and anakinra. Tocilizumab is preferred at JHHS because of considerably more clinical experience with this agent.

In the EMPACTA,[33] REMAP-CAP,[34] and RECOVERY[35] studies of tocilizumab (see below), in which most 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.[36] 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 the futility of demonstrating a difference between arms (see NIH closes enrollment in a 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.[37] 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.[38]

No studies are available comparing head-to-head targeted immunomodulatory agents, nor are studies available assessing the use of multiple targeted immunomodulatory agents. These agents may be equivalent, or an agent may have an advantage in specific clinical scenarios. Because of the greater clinical experience and the number of RCTs involving tocilizumab, this writing group generally favors the use of tocilizumab if treatment with a targeted immunomodulatory agent is necessary.

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.[39]
- 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[40] or clinical progression at 14 days[41]; 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 those who received a placebo (9% and 35%, respectively).[42]
- 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).[43,44]

Tocilizumab with extensive use (>70% at randomization) of corticosteroids:

- **EMPACTA:** The Roche EMPACTA study of tocilizumab reported a reduction in mechanical ventilation in a double-blind RCT of 389 participants with COVID-19 pneumonia.[45] 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.[46,47]
- **REMAP-CAP:** This international adaptive clinical trial platform tested multiple COVID-19 therapeutics and examined tocilizumab or sarilumab compared with standard care.[34] Participants were adults with COVID-19 admitted to an ICU who received respiratory or cardiovascular support through 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 usual care arm. Both outcomes were significant based on Bayesian statistical analysis.
- **RECOVERY:** This multi-site factorial design RCT in the United Kingdom included a tocilizumab treatment arm.[35] 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.
- **Brazil study:** An RCT conducted in Brazil enrolled 129 adult participants with COVID-19 to receive tocilizumab or standard care.[16] 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).

Convalescent Plasma (for Immunosuppressed Patients)

Early RCTs: Early RCTs of convalescent plasma treatment, which enrolled participants ≥ 1 week after symptom onset when many had already developed neutralizing antibodies, failed to show a benefit.[48-53] The trials reported below with earlier administration displayed clinical efficacy.

- A placebo-controlled RCT from Argentina randomized 160 ambulatory participants aged ≥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.[54] At day 15, more participants in the placebo arm (31%) than in the convalescent plasma arm (16%) developed severe respiratory disease (*P*=.02).
- An RCT with 1,181 ambulatory participants ≥18 years old, recruited regardless of comorbidities or vaccination status (17% were partially or wholly vaccinated), compared 28-day hospitalization rates among those who received high-titer

convalescent plasma or control plasma.[55] In the pre-specified 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).

EAP studies: 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.[56] 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.[56] 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).[57]
- A large retrospective study from HCA Healthcare included 4,337 participants who received convalescent plasma and 8,708 who did not report lower mortality in those who received convalescent plasma (hazard ratio, 0.71; *P*<.001). A difference in mortality was observed for those who received convalescent plasma within 3 days of hospital admission but not among those who received it 4 to 7 days after admission.[58]

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*).[59] Clinical efficacy studies have not been 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.[60] 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.[61]

Benefits: As noted above, the benefit is most likely 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[54,55]).

Risks: The risks associated with the use of convalescent plasma include a very low risk of pathogen transmission (~1 in 2 million units),[62-64] allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.[63,64] A review of convalescent plasma therapy for severe or life-threatening COVID-19 in 5,000 participants in the United States found that serious adverse events at 4 hours post-administration occurred in <1%.[65] 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,[66] 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 TACO in 0.10%. These analyses provide evidence for convalescent plasma therapy's safety but not efficacy for patients with severe COVID-19.

B. Alternative Agents

Molnupiravir (Lagevrio)

In the MOVe-OUT trial, at-risk, non-hospitalized adults (≥18 years old) with ≤5 days of symptoms were randomized to receive either molnupiravir 800 mg twice daily or placebo for 5 days.[67] 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.

Baricitinib (Olumiant)

- **ACTT-2:** This 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.[68] The ACTT-4 study compared 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 received low-flow oxygen, high-flow oxygen, or noninvasive mechanical ventilation on enrollment; 75% received dexamethasone before 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.[69]
- **COV-BARRIER:** 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.[70] 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 received mechanical ventilation or ECMO and had elevated inflammatory markers.[37] 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.
- **RECOVERY:** 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.[71] 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).

Anakinra (Kineret)

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.

- 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.[72]
- The SAVE non-randomized study[73] 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 a placebo (0.5%). On November 8, 2022, the FDA issued an EUA for anakinra to treat severe COVID-19 in hospitalized patients.

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.[74,75]

- 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.[76] 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.[76] 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. Agents to Avoid

Vilobelimab

This chimeric human-mouse IgG4 kappa anti-C5a monoclonal antibody is available through an FDA EUA to treat hospitalized patients with severe COVID-19 disease who receive mechanical ventilation or in whom ECMO has been initiated within the past 48 hours. However, because there is insufficient evidence to support the routine use of this agent in any population with COVID-19, this writing group does not recommend the use of this agent.

The FDA EUA approval is based on results from 2 studies:

- An open-label exploratory study with 30 participants randomized to vilobelimab or standard care suggested lower mortality among those receiving vilobelimab (13% versus 27% mortality, not significant).[77]
- A follow-up multi-site international placebo-controlled RCT enrolled 368 adult participants (before Omicron) on invasive mechanical ventilation or ECMO for less than 48 hours; 17% received IL6 antagonists, and 97% received glucocorticoids.[78] Mortality was 31% in the vilobelimab arm compared to 40% in the placebo arm (p=0.094). In the predefined analysis without site-stratification, vilobelimab significantly reduced all-cause mortality at 28 days (HR 0·67, 95% CI 0·48–0·96; p=0·027). In subgroup analysis, vilobelimab appeared to perform best among individuals receiving invasive mechanical ventilation and renal replacement therapy. Criticisms of the applicability of the study include low use of anti-IL6 agents and considerable variation in outcomes by site, with those who received tocilizumab in Western Europe potentially driving the mortality numbers and not vilobelimab. We believe insufficient evidence exists for the routine use in any population with COVID-19.

Metformin

- A pre-specified secondary outcome of the COVID-OUT study comparing each fluvoxamine, ivermectin, and metformin to placebo reported a reduction in post-COVID-19 symptoms to day 180 post-randomization among the group receiving metformin when compared to placebo.[79] The self- or clinician-reported incidence of post-COVID-19 symptoms was 6.3% among participants who received metformin and 10.4% among those who received placebo (hazard ratio 0.59, p=0.012). There was no effect on post-COVID-19 symptoms from fluvoxamine or ivermectin compared to placebo.
- This agent has been explored for outpatient use (COVID-OUT) in participants aged 30 to 85 years old who were obese, not currently taking metformin for diabetes, and had symptom onset within the previous days; 1.9% had diabetes. Among participants in a 6-arm RCT in an outpatient setting comparing metformin, fluvoxamine, and ivermectin to placebo, no difference in the primary composite outcome (hypoxemia by pulse oximetry, ED visits, hospitalization, or death) was observed by arm among the 1,323 participants.[80] There was a reduction in emergency department visits, hospitalization, or death among those receiving metformin: adjusted odds ratio 0.58 (0.35-0.94).
- In the TOGETHER trial (14.6% of participants had diabetes; taking oral medications not excluded) conducted in Brazil, 418 ambulatory participants at higher risk for severe COVID-19 were randomized to metformin or placebo.[81] The trial was

halted due to futility, with 13% of the metformin arm and 15% of the placebo arm participants meeting the primary outcome of hospitalization. These primary outcomes suggest that metformin does not appear to have a role in the acute outpatient management of COVID-19.

IV. COVID-19 Treatment in 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.[1,2,9-12] This effect is analogous to other viruses (e.g., influenza, norovirus, respiratory syncytial virus) in patients with substantial immunodeficiency who cannot clear acute viral infections.[82,83] 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,[9,10] in which 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.[9,13,14] Integrating Ct values into the clinical assessment may offer supportive evidence of ongoing SARS-CoV-2 replication causing disease (e.g., Ct ≤30 cycles).[9,14] In solid organ transplant recipients and others with severe immunodeficiency, it appears that productive SARS-CoV-2 viral infection may routinely extend to day 21, which is a longer duration than that observed in non-immunocompromised populations.[9,10] Sometimes, the duration may be much longer than 21 days. The non-standardized surrogate (Ct value) is employed only because there is no routinely available clinical laboratory testing currently available to conclusively distinguish between ongoing replication and the presence of SARS-CoV-2 RNA without replication.

Although the optimal treatment duration in these patients has yet to be defined, antiviral treatment is appropriate when ongoing viral replication is suspected or confirmed. The presence or absence of SARS-CoV-2-specific antibodies is irrelevant 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 and avoid the emergence of resistance with monotherapy, clinicians may consider combination treatment with RDV or nirmatrelvir/ritonavir (or molnupiravir if neither nirmatrelvir/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. Robust clinical data are needed to back a formal recommendation; however, some limited case descriptions and animal model data suggest an efficacious approach.[84,85]

V. Development of This Guideline

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 3: COVID-19 Pharmacologic Treatment Guidance Writing Group

- **Chair:** Paul G. Auwaerter, MD, MBA, Clinical Director, Division of Infectious Diseases; Professor of Medicine
- **Lead author:** Christopher J. Hoffmann, MD, MPH, Associate Professor of Medicine, Department of Medicine, Division of Infectious Diseases
- **Editor:** Mary Beth Hansen, MA, JHU/NYSDOH Clinical Guidelines Program Director

Contributing members:

- Robin K. Avery, MD, Professor of Medicine
- Richard F. Ambinder, MD, PhD, Director, Division of Hematologic Malignancies; Professor of Oncology
- Andrew M. Cameron, MD, PhD, Chief, Division of Transplantation; Professor of Surgery
- Larry W. Chang, MD, MPH, Associate Professor of Medicine, Department of Medicine, Division of Infectious Diseases

Box 3: COVID-19 Pharmacologic Treatment Guidance Writing Group

- Natasha M. Chida, MD, MSPH, Associate Director, Infectious Diseases Fellowship Program; Assistant Professor of Medicine
- Rebecca H. Dezube, MD, MHS, Assistant Professor of Medicine, Pulmonary and Critical Care Medicine; Medical Director, COVID Faculty
- Kate Dzintars, PharmD, Clinical Pharmacy Specialist, Division of Infectious Disease
- Brian T. Garibaldi, MD, Director, Johns Hopkins Biocontainment Unit; Associate Professor of Medicine
- Elisa Ignatius, MD, MSc, Fourth Year Fellow, Infectious Diseases, Clinical Pharmacology
- Andrew Karaba, MD, PhD, Assistant Professor of Medicine, Division of Infectious Diseases
- Maria Veronica Dioverti Prono, MD, Assistant Professor of Medicine
- Pali D. Shah, MD, Medical Director, Johns Hopkins Lung Transplantation; Assistant Professor of Medicine
- R. Scott Stephens, MD, Director, Oncology and Bone Marrow Transplant Critical Care; Associate Professor of Medicine and Oncology
- David J. Sullivan Jr, MD, Professor, Molecular Microbiology and Immunology; Joint appointment in Medicine
- Ethel D. Weld, MD, PhD, Assistant Professor of Medicine, Pharmacology, and Molecular Sciences; Clinical Pharmacology, Infectious Diseases

A smaller writing group was convened from the larger working group 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 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 designs and adequate sample size are considered the best possible data source 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 range from providing drugs only within a therapeutic trial to providing drugs with theoretical but possible benefits if risks of adverse reactions are deemed acceptable.
- The writing group recommends that prescribing clinicians consult with infectious diseases clinicians to treat any recipient of or candidate for a solid organ or bone marrow transplant. Consultation with infectious diseases clinicians for evaluation or management of any hospitalized patient with suspected (person under investigation [PUI]) or confirmed COVID-19 is otherwise up to the judgment and needs of the primary care team.

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

References

1. Truong TT, Ryutov A, Pandey U, et al. Persistent SARS-CoV-2 infection and increasing viral variants in children and young adults with impaired humoral immunity. medRxiv. 2021. https://www.ncbi.nlm.nih.gov/pubmed/33688673
2. Nakajima Y, Ogai A, Furukawa K, et al. Prolonged viral shedding of SARS-CoV-2 in an immunocompromised patient. *J Infect Chemother.* 2021;27(2):387-389. https://www.ncbi.nlm.nih.gov/pubmed/33328135
3. He X, Lau EHY, Wu P, et al. Author Correction: Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med.* 2020;26(9):1491-1493. https://pubmed.ncbi.nlm.nih.gov/32770170/
4. Sachithanandham J, Thio CL, Balagopal A. The natural history of severe acute respiratory syndrome coronavirus 2 infection: A composite but incomplete picture. *Clin Infect Dis.* 2020;73(9):e2943-e2945. https://pubmed.ncbi.nlm.nih.gov/33090197/
5. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med.* 2020;26(5):672-675. https://pubmed.ncbi.nlm.nih.gov/32296168/
6. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med.* 2020;180(9):1156-1163. https://pubmed.ncbi.nlm.nih.gov/32356867/
7. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe.* 2021;2(1):e13-e22. https://pubmed.ncbi.nlm.nih.gov/33521734/
8. Dioverti V, Salto-Alejandre S, Haidar G. Immunocompromised patients with protracted COVID-19: a review of "long persisters." *Curr Transplant Rep.* 2022;9(4):209-218. https://pubmed.ncbi.nlm.nih.gov/36407883/
9. Buckland MS, Galloway JB, Fhogartaigh CN, et al. Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report. *Nat Commun.* 2020;11(1):6385. https://www.ncbi.nlm.nih.gov/pubmed/33318491
10. Camprubi D, Gaya A, Marcos MA, et al. Persistent replication of SARS-CoV-2 in a severely immunocompromised patient treated with several courses of remdesivir. *Int J Infect Dis.* 2021;104:379-381. https://www.ncbi.nlm.nih.gov/pubmed/33359065
11. Kemp SA, Collier DA, Datir RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. *Nature.* 2021;592(7853):277-282. https://www.ncbi.nlm.nih.gov/pubmed/33545711
12. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? *Clin Infect Dis.* 2021;72(8):1467-1474. https://www.ncbi.nlm.nih.gov/pubmed/33029620
13. Rao SN, Manissero D, Steele VR, Pareja J. A systematic review of the clinical utility of cycle threshold values in the context of COVID-19. *Infect Dis Ther.* 2020;9(3):573-586. https://www.ncbi.nlm.nih.gov/pubmed/32725536
14. Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro Surveill.* 2020;25(32). https://www.ncbi.nlm.nih.gov/pubmed/32794447
15. Breeden M, Aitken SL, Baang JH, et al. Successful treatment of prolonged severe acute respiratory syndrome coronavirus 2 infection in patients with immunodeficiency with extended nirmatrelvir/ritonavir: case series. *Open Forum Infect Dis.* 2023;10(4):ofad189. https://pubmed.ncbi.nlm.nih.gov/37089775/
16. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ.* 2021;372:n84. https://pubmed.ncbi.nlm.nih.gov/33472855/
17. Casarola G, D'Abbondanza M, Curcio R, et al. Efficacy of convalescent plasma therapy in immunocompromised patients with COVID-19: a case report. *Clin Infect Pract.* 2021;12:100096. https://pubmed.ncbi.nlm.nih.gov/34490417/
18. Brown LK, Moran E, Goodman A, et al. Treatment of chronic or relapsing COVID-19 in immunodeficiency. *J Allergy Clin Immunol.* 2022;149(2):557-561.e551. https://pubmed.ncbi.nlm.nih.gov/34780850/

19. Hueso T, Pouderoux C, Péré H, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood.* 2020;136(20):2290-2295. https://pubmed.ncbi.nlm.nih.gov/32959052/

20. Ford ES, Simmons W, Karmarkar EN, et al. Successful treatment of prolonged, severe coronavirus disease 2019 lower respiratory tract disease in a B cell acute lymphoblastic leukemia patient with an extended course of remdesivir and nirmatrelvir/ritonavir. *Clin Infect Dis.* 2023;76(5):926-929. https://pubmed.ncbi.nlm.nih.gov/36326680/

21. Mikulska M, Sepulcri C, Dentone C, et al. Triple combination therapy with 2 antivirals and monoclonal antibodies for persistent or relapsed severe acute respiratory syndrome coronavirus 2 infection in immunocompromised patients. *Clin Infect Dis.* 2023;77(2):280-286. https://pubmed.ncbi.nlm.nih.gov/36976301/

22. Zhang AW, Morjaria S, Kaltsas A, et al. The effect of neutropenia and filgrastim (G-CSF) on cancer patients with coronavirus disease 2019 (COVID-19) infection. *Clin Infect Dis.* 2022;74(4):567-574. https://pubmed.ncbi.nlm.nih.gov/34111237/

23. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - Final report. *N Engl J Med.* 2020;383(19):1813-1826. https://pubmed.ncbi.nlm.nih.gov/32445440/

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

25. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis.* 2022;22(2):209-221. https://www.ncbi.nlm.nih.gov/pubmed/34534511

26. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med.* 2022;386(305-315). https://pubmed.ncbi.nlm.nih.gov/34937145/

27. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med.* 2021;384(8):693-704. https://pubmed.ncbi.nlm.nih.gov/32678530/

28. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: An open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr.* 2021;133(7-8):303-311. https://pubmed.ncbi.nlm.nih.gov/33534047/

29. Jung C, Wernly B, Fjolner J, et al. Steroid use in elderly critically ill COVID-19 patients. *Eur Respir J.* 2021;58(4):2100979. https://www.ncbi.nlm.nih.gov/pubmed/34172464

30. Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. *JAMA.* 2020;324(13):1330-1341. https://pubmed.ncbi.nlm.nih.gov/32876694/

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

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

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

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

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

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

37. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane

oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med.* 2022;10(4):327-336. https://pubmed.ncbi.nlm.nih.gov/35123660/

38. Temesgen Z, Burger CD, Baker J, et al. Preprint: Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: results from the LIVE-AIR phase 3 randomized double-blind placebo-controlled trial. *medRxiv.* 2021. https://www.ncbi.nlm.nih.gov/pubmed/33972949
39. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med.* 2020;383(24):2333-2344. https://pubmed.ncbi.nlm.nih.gov/33085857/
40. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized clinical trial. *JAMA Intern Med.* 2021;181(1):32-40. https://pubmed.ncbi.nlm.nih.gov/33080017/
41. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. *JAMA Intern Med.* 2021;181(1):24-31. https://pubmed.ncbi.nlm.nih.gov/33080005/
42. Mariette X, Hermine O, Tharaux PL, et al. Effectiveness of tocilizumab in patients hospitalized with COVID-19: A follow-up of the CORIMUNO-TOCI-1 randomized clinical trial. *JAMA Intern Med.* 2021;181(9):1241-1243. https://pubmed.ncbi.nlm.nih.gov/34028504/
43. Roche. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Published 2020. Updated July 29, 2020. Accessed August 10, 2020.
44. ClinicalTrials.gov. A study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACTA). https://clinicaltrials.gov/ct2/show/NCT04320615. Published 2021. Updated June 30, 2021. Accessed August 10, 2020.
45. Roche. Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia. https://www.roche.com/media/releases/med-cor-2020-09-18.htm. Published 2020. Updated September 18, 2020. Accessed October 6, 2020.
46. Sanofi. Press release: Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00. Published 2020. Updated July 2, 2020. Accessed August 10, 2020.
47. ClinicalTrials.gov. Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19. https://clinicaltrials.gov/ct2/show/NCT04315298. Published 2021. Updated September 23, 2021. Accessed August 10, 2020.
48. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. *JAMA.* 2020;324(5):460-470. https://pubmed.ncbi.nlm.nih.gov/32492084/
49. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. *Nat Commun.* 2021;12(1):3189. https://pubmed.ncbi.nlm.nih.gov/34045486/
50. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med.* 2021;27(11):2012-2024. https://pubmed.ncbi.nlm.nih.gov/34504336/
51. Avendaño-Solá C, Ramos-Martínez A, Muñez-Rubio E, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. *J Clin Invest.* 2021;131(20):e152740. https://pubmed.ncbi.nlm.nih.gov/34473652/
52. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med.* 2021;384(7):619-629. https://pubmed.ncbi.nlm.nih.gov/33232588/
53. Writing Committee for the REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA.* 2021;326(17):1690-1702. https://www.ncbi.nlm.nih.gov/pubmed/34606578

54. Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med.* 2021;384(7):610-618. https://pubmed.ncbi.nlm.nih.gov/33406353/

55. Sullivan DJ, Gebo KA, Shoham S, et al. Early outpatient treatment for Covid-19 with convalescent plasma. *N Engl J Med.* 2022;386(18):1700-1711. https://pubmed.ncbi.nlm.nih.gov/35353960/

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

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

58. Arnold Egloff SA, Junglen A, Restivo JS, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. *J Clin Invest.* 2021;131(20):e151788. https://pubmed.ncbi.nlm.nih.gov/34464352/

59. NIH. OpenData Portal: SARS-CoV-2 Variants & Therapeutics: Therapeutic Activity Explorer. https://opendata.ncats.nih.gov/variant/activity. Published 2022. Updated November 7, 2022. Accessed November 22, 2022.

60. Schmidt F, Muecksch F, Weisblum Y, et al. Plasma neutralization properties of the SARS-CoV-2 Omicron variant. *medRxiv.* 2021. https://pubmed.ncbi.nlm.nih.gov/34931199/

61. Cele S, Gazy I, Jackson L, et al. Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. *Nature.* 2021;593(7857):142-146. https://pubmed.ncbi.nlm.nih.gov/33780970/

62. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest.* 2020;30(6):2757-2765. https://www.ncbi.nlm.nih.gov/pubmed/32254064

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

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

65. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. *J Clin Invest.* 2020;130(9):4791-4797. https://www.ncbi.nlm.nih.gov/pubmed/32525844

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

67. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med.* 2022;386(6):509-520. https://pubmed.ncbi.nlm.nih.gov/34914868/

68. Eli Lilly and Company. News reslease: Baricitinib in combination with remdesivir reduces time to recovery in hospitalized patients with COVID-19 in NIAID-sponsored ACTT-2 trial. https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery. Published 2020. Updated September 14, 2020. Accessed October 7, 2020.

69. Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med.* 2022;10(9):888-899. https://pubmed.ncbi.nlm.nih.gov/35617986/

70. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med.* 2021;9(12):1407-1418. https://pubmed.ncbi.nlm.nih.gov/34480861/

71. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet.* 2022;400(10349):359-368. https://pubmed.ncbi.nlm.nih.gov/35908569/

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

73. Kyriazopoulou E, Panagopoulos P, Metallidis S, et al. An open label trial of anakinra to prevent respiratory failure in COVID-19. *Elife.* 2021;10. https://www.ncbi.nlm.nih.gov/pubmed/33682678

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

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

76. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet.* 2020;395(10238):1695-1704. https://www.ncbi.nlm.nih.gov/pubmed/32401715

77. Vlaar APJ, de Bruin S, Busch M, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. *Lancet Rheumatol.* 2020;2(12):e764-e773. https://pubmed.ncbi.nlm.nih.gov/33015643/

78. Vlaar APJ, Witzenrath M, van Paassen P, et al. Anti-C5a antibody (vilobelimab) therapy for critically ill, invasively mechanically ventilated patients with COVID-19 (PANAMO): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med.* 2022;10(12):1137-1146. https://pubmed.ncbi.nlm.nih.gov/36087611/

79. Faust JS. The therapeutic validation of long COVID. *Lancet Infect Dis.* 2023. https://pubmed.ncbi.nlm.nih.gov/37302405/

80. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for Covid-19. *N Engl J Med.* 2022;387(7):599-610. https://pubmed.ncbi.nlm.nih.gov/36070710/

81. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health.* 2022;10(1):e42-e51. https://www.ncbi.nlm.nih.gov/pubmed/34717820

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

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

84. Jeong JH, Chokkakula S, Min SC, et al. Combination therapy with nirmatrelvir and molnupiravir improves the survival of SARS-CoV-2 infected mice. *Antiviral Res.* 2022;208:105430. https://pubmed.ncbi.nlm.nih.gov/36209984/

85. Li P, Wang Y, Lavrijsen M, et al. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. *Cell Res.* 2022;32(3):322-324. https://pubmed.ncbi.nlm.nih.gov/35058606/

Appendix A: Paxlovid Formulary Addition Memorandum

1/11/2023

JOHNS HOPKINS
MEDICINE

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,

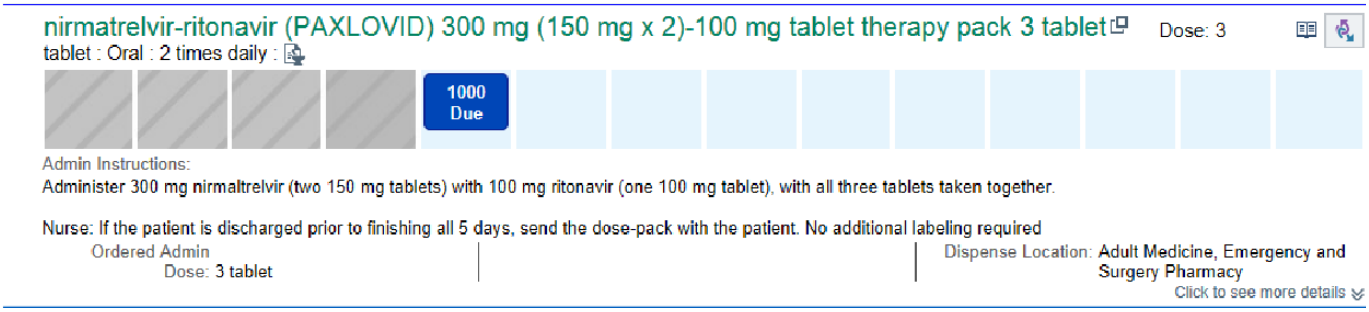
On November 30th, 2022, the FDA revoked the emergency use authorization (EUA) for bebtelovimab. As a result of that decision, Paxlovid (nirmatrelvir/ritonavir) was added to the JHHS Formulary. Hospitalized patients with symptomatic mild-to-moderate COVID-19, who were not hospitalized due to COVID-19, 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 B: Non-Oncology Remdesivir Referral Workflow

1/9/2023

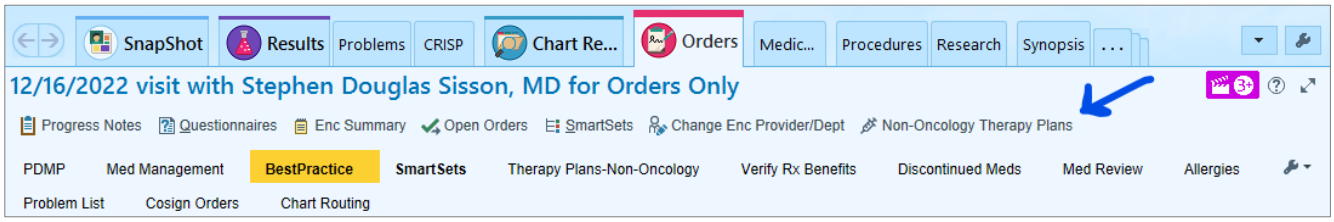
Introduction

- 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*.
- 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.

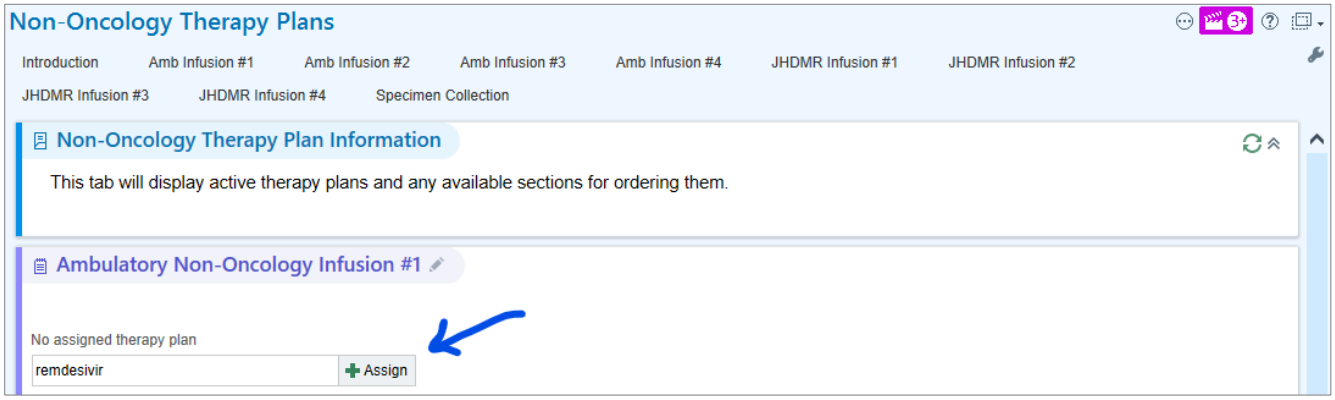
Ordering Instructions

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 for ambulatory patients with liver enzymes greater than 5X the upper limit of normal**.



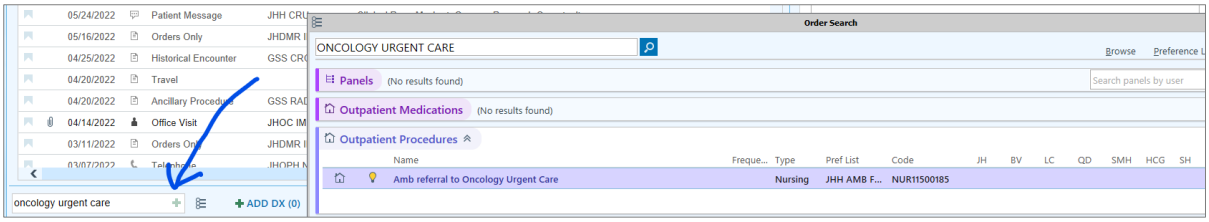
3. Once the therapy plan is submitted, send a simultaneous email to adultivinfusion@jhmi.edu to alert them to the patient. The Park Infusion team will reach out to the patient to schedule and provide instructions to the patient.

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 5X the upper limit of normal:

- Notify the patient that no further infusions shall be administered and cancel the remainder of the therapy plan.
- Notify the Park Infusion team through email at adultivinfusion@jhmi.edu.
- 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.

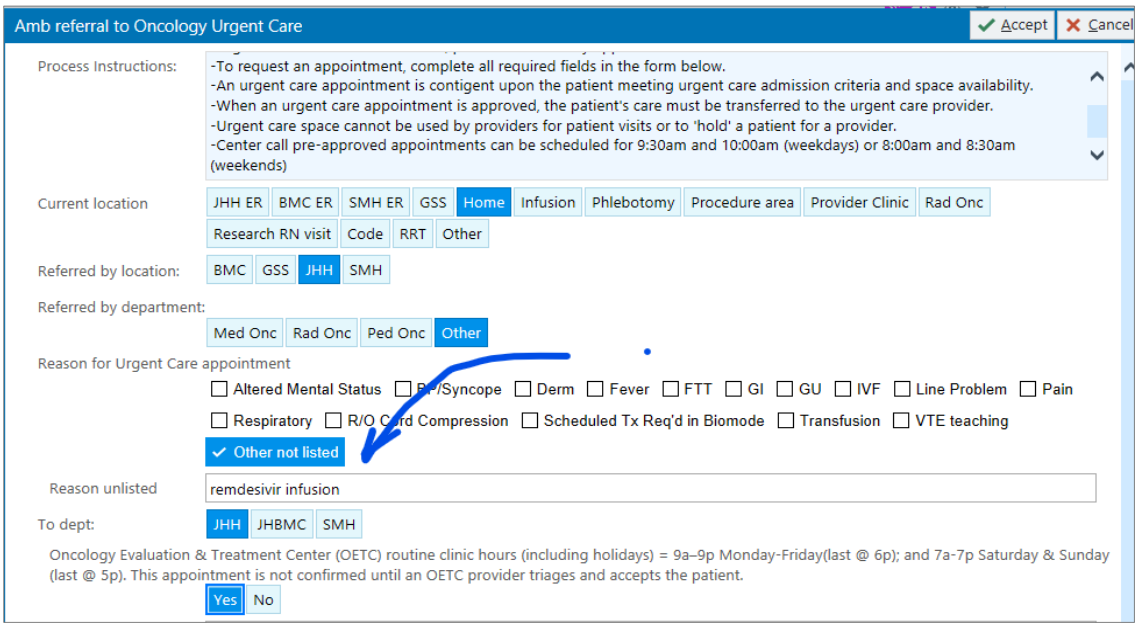
5. If the 3-day infusion course includes a weekend or holiday, you will need to refer the patient to Oncology Urgent Care as described below. Oncology will assume care of the referred patient on weekends and holidays.

Weekend or 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.