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

Source: JHH COVID-19 Treatment Guidance Writing Group
Date: February 12, 2026; replaces the last update of July 16, 2025

New in This Update: January 28, 2026
▪ Removal of 3 day course of Remdesivir (RDV) as a treatment option for patients at high-risk of severe COVID-19. ▪ Update on metformin and use in COVID-19: not recommended outside of a clinical trial

Contents

I. COVID-19 Treatment Rapid Reference

Figure 1: Rapid Reference for Treatment of COVID-19 in Immunocompetent [a] Adults at Risk of or With Severe Disease [b,c]

Outpatient treatment or inpatient treatment for an immunocompetent patient hospitalized but not primarily for COVID-19 and at risk of severe disease	Inpatient treatment of a patient hospitalized with severe COVID-19 (SaO2 <94%)	
Symptoms ≤5 days: ▪ NRM/r PO twice daily for 5 days (if unable to receive NRM/r consider RDV IV x 5d for those at exceptional risk)[d]	DEX 6 mg IV or PO daily for 10 days or until d/c *plus*	
	Symptoms ≤7 days: RDV IV for 5 days (day 1: 200 mg; days 2 through 5: 100 mg/day) ▪ d/c if patient is discharged before day 5 ▪ Consider 5 additional days of RDV IV if no improvement	**CRP >7.5 mg/dL [e] and high-flow O_2 or intensive care for ≤24 hours:** BAR 4 mg PO once per day for 14 days [f] + RDV for 10 days

Abbreviations: BAR, baricitinib; CRP, C-reactive protein; d/c, discontinue; DEX, dexamethasone; IV, intravenous; RDV, remdesivir; NRM/r, nirmatrelvir/ritonavir; SaO2, oxygen saturation; PO, by mouth; TCZ, tocilizumab

Notes:

a. Refer to Table 1 for guidance for immunosuppressed adults
b. Refer to Tables 1 and 2, as well as the text, for further guidance, details, and justification.
c. For highly immunocompromised patients, consult with Transplant and Oncology Infectious Diseases service regarding management, including the potential use of convalescent plasma.
d. May include multiple comorbidities, severe lung disease, and very advanced age
e. CRP is not required for immunocompromised patients.
f. TCZ is an alternative. Non-formulary approval is required for the use of TCZ or BAR.

II. 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-2 disease 2019 (COVID-19). This guidance is based on current knowledge, experience, and expert opinion, with the caveat that interpretation of studies from early in the pandemic is now influenced by our recognition of the background immunity present in nearly all people. The goal is to establish a standardized approach to the use of pharmacologic agents in patients diagnosed with COVID-19.

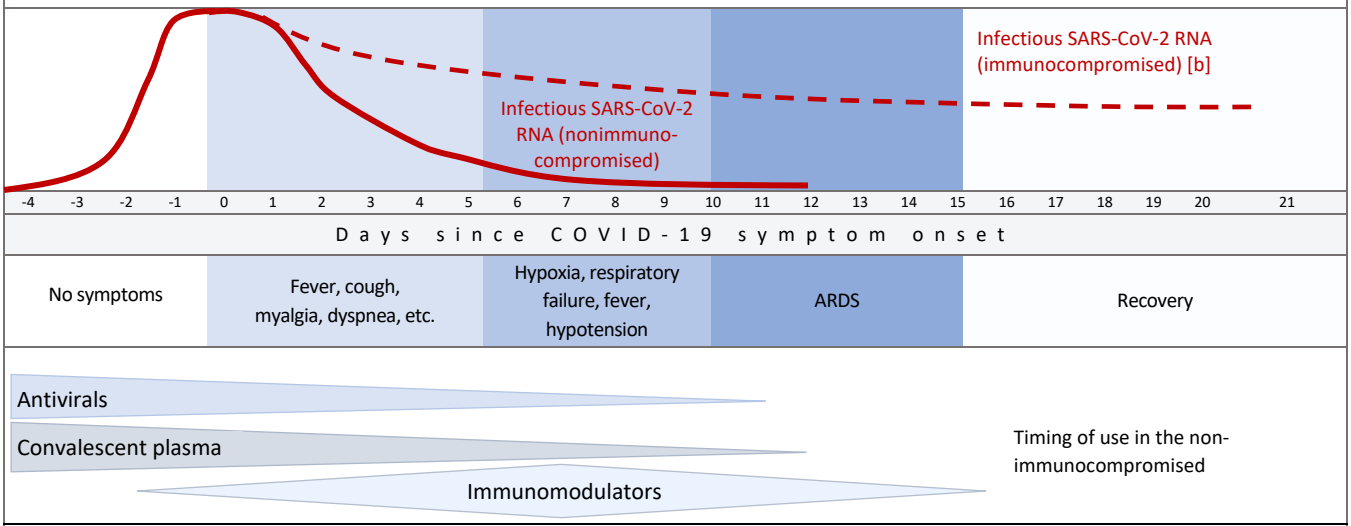
A. Approaches to Treatment

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, COVID-19 convalescent plasma, and immunomodulatory therapies can alter the course of the disease by reducing severity and 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 2. 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 period), common symptoms, and possible timing of therapeutics for the most significant benefit. Symptoms and viral shedding may be prolonged in some patients who are substantially immunocompromised. Below, the red lines illustrate the typical trends for SARS-CoV-2 RNA levels in individuals who are and are not immunocompromised. [a]



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

Notes:

a. Viral variants may have a more extended period of infectious virus, i.e., >10 days in normal hosts.[1-7]

b. In immunocompromised individuals, the duration is variable, especially in those who are 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 most substantial 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? At this point since the emergence of SARS-CoV-2, most people have either been vaccinated, had COVID-19, or both.

Pregnancy: Since COVID-19 infection carriers have higher risks of severe disease, including ICU care, mechanical ventilation, stillbirth and preterm labor, early antiviral therapy is advocated for symptomatic patients and also endorsed by the American College of Obstetricians and Gynecologists. Treatment with specific agents should be discussed as part of shared decision-making among the patient, obstetrician, and consultants. If pregnant patients meet criteria for treatment, do not withhold therapy on the basis of gestational age alone (see ACOG FAQs: https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics).

- Remdesivir: Substantial observational data, as well as registries and use for Ebola, find no teratogenicity signal for RDV, which has limited placental transfer and is considered compatible for breastfeeding.
- Nirmatrelvir/ritonavir: This oral protease inhibitor has no known teratogenic effects observed with animal data, and experience with pregnancy HIV/AIDS has shown a known increased risk of congenital defects or low birth weights.
- Tocilizumab: limited case series/reports suggest successful maternal/fetal outcomes; however, due to rather limited pregnancy data, it is typically reserved only for severe, life-threatening COVID-19.
- COVID-19 convalescent plasma: CCP is considered safe during pregnancy.
- **Avoid:**
    - Baricitinib: animal data suggest embryofetal toxicity at high doses. Given the very limited COVID-19 experience in pregnant patients without the ability to judge fetal risk, tocilizumab is preferred as an additional immunomodulator to corticosteroids.
    - Molnupiravir: animal data show a significant risk of fetal harm, and there is a lack of human safety data.

III. 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.
- Use DEX 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 baricitinib (BAR) to antiviral therapy and DEX in patients with clinical progression (see below) after DEX initiation.
- 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.
- 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.[8]
- See Table 2 and Section C for care of immunocompromised patients**.**

Avoid the use of:

- **Vilobelimab:** Insufficient evidence to support routine use as a treatment for COVID-19 in any population;[9,10] The pivotal trial on which the FDA based its EUA included a substantial number of participants also receiving TCZ.
- **Clinical trial data indicate no substantial benefit or potential harm:** Azithromycin, colchicine, DAS 181, hydroxychloroquine, ivermectin, nitazoxanide, oseltamivir, vitamin D, and zinc.

Box 2: Summary of Clinical Recommendations for Pharmacologic Treatment of COVID-19 in Adults
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; NRM, nirmatrelvir; NRM/r, nirmatrelvir/ritonavir; RCT, randomized controlled trial; RDV, remdesivir; RTV, ritonavir; SaO_2, saturation of arterial blood; tocilizumab, TCZ

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

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

Preferred Agents			
Remdesivir (RDV; Veklury)			
JHHS recommends the treatment of: ▪ Ambulatory patients ≤7 days of COVID-19 symptoms with immunodeficiency [a] ▪ RDV is not recommended for ambulatory patients or hospitalized patients with mild COVID-19 and without immunodeficiency (see below for treatment of severe COVID-19) ▪ See clinical trials	**Administration and duration**: 5-day course ▪ Infusion day 1: 200 mg IV loading dose ▪ Infusion days 2 and5: 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 restart 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 ▪ The 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 levels	**Notes:** ▪ FDA-approved ▪ No dose adjustment is required with impaired liver or kidney function ▪ Daily AST and ALT monitoring is recommended ▪ May be considered for use in pregnancy **Ambulatory patients:** ▪ Nirmatrelvir/RTV is preferred. ▪ Oncology patients can obtain an infusion through the OETC. ▪ All non-oncology patients should obtain an infusion at Park Infusion. Referrals are processed on weekdays only. Place a "non-oncology therapy plan" in EPIC and send a message to adultinfusion@jhmi.edu.
Nirmtrelvir/ritonavir (NRM/r; 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:**	**Administration and duration:** ▪ NRM 300 mg/RTV 100 mg by mouth twice daily for 5 days ▪ Use reduced dose if eGFR 30-60 mL/min: 150 mg/ 100 mg by mouth twice daily x 5 days ▪ Not authorized for >5 consecutive days of 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 a clinical pharmacologist as needed • Also see: Liverpool COVID-19 Drug Interactions Checker ▪ The most common adverse effects include dysgeusia and diarrhea	**Notes:** ▪ FDA-approved ▪ 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; for treated patients, additional courses of treatment are not indicated. **JHMI requirements:**

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

▪ 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			▪ Do not use for patients requiring oxygen for COVID-19 illness (see Appendix A) ▪ Check for drug interactions; If drug interactions preclude use of nirmtrelvir/ritonavir, and patient is at high risk for severe COVID-19, then RDV x 5 days warranted. ▪ Order through Epic
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 ▪ The 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; OETC, oncology evaluation and treatment center; NRM/r, nirmatrelvir/ritonavir; PCR, polymerase chain reaction; P&T, Pharmacy & Therapeutics Committee; RDV, remdesivir.

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. Inpatient Treatment of Adults with Severe COVID-19 or who are immunnosuppressed with COVID-19

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

Preferred Agents

Remdesivir (RDV; Veklury)

JHHS recommends the treatment of:	Administration and duration:	Cautions and adverse effects:	Notes:
▪ Non-immunosuppressed patients hospitalized with COVID-19 with ≤7 days of symptoms and supplemental O_2 requirement or ≤24 hours of ECMO or mechanical ventilation ▪ Highly immunosuppressed [a] patients: Any O_2 requirement and ICU care are allowed. RDV may be started 10 days after symptom onset.	▪ **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].	▪ 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 restart 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 ▪ The 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 levels	▪ Daily AST and ALT monitoring is recommended ▪ May be considered for use in pregnancy ▪ Do not admit to the hospital or delay discharge for RDV administration ▪ A 3-day RDV infusion is no longer recommended or included in the JHHS formulary.

Dexamethasone (DEX)

JHHS recommends the treatment of:	Administration and duration:	Cautions and adverse effects:	Note:
▪ Patients with SaO2 <94% or in the ICU ▪ See clinical trials	▪ 6 mg IV or oral once daily for up to 10 days or until hospital discharge	▪ 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	▪ Can substitute another corticosteroid if DEX is unavailable

Baricitinib (BAR; Olumiant)

JHHS recommends the treatment of:		Cautions and adverse effects:	Notes:
▪ Hospitalized patients (including ICU for ≤24 hours) with severe COVID-19 with CRP >7.5 mg/dl who require supplemental O2 (escalating O2 requirements, non-invasive or invasive mechanical ventilation or ECMO) for COVID-19 management despite use of DEX ▪ Patients in whom corticosteroids are contraindicated as a substitute for DEX	▪ **Administration and duration:** 4 mg enterally daily for 14 days (maximum)	▪ Results from animal studies raised concerns for use in pregnancy; see text ▪ Adverse events include elevation in ALT and hypersensitivity reactions	▪ FDA approved (2022) for severe COVID-19 pneumonia ▪ Preferred by this COVID-19 Treatment Guidance Committee over tocilizumab (except in pregnancy) **JHMI requirement:** ▪ Non-formulary approval required ▪ Elevated CRP is not required for non-formulary approval for immunocompromised patients

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

COVID-19 Convalescent Plasma With High-Titer SARS-CoV-2 Antibodies (consult with infectious diseases)

JHHS recommends the treatment of:	Administration and duration:	Cautions and adverse effects:	Notes:
▪ Hospitalized patients with or without O_2 requirement who are immunosuppressed [a] or receiving immunosuppressive therapy ▪ Ambulatory patients who are immunosuppressed [a]	▪ CCP is FDA-approved (Dec 2024) for COVID-19 and is available for transfusion medicine use via an EPIC order set. ▪ IV infusion, initiate with 2 units (200-300 mL/unit), Consider spacing units > 1 day apart, especially if at risk of volume overload. ▪ Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times. ▪ Additional units (e.g., 2 to 3 with units given daily or every other day) may be administered based on the patient's clinical response ▪ Plasma ABO compatibility: Discuss with Transfusion Medicine.	▪ Minimal adverse events have been reported from clinical trials, although transfusion reactions are possible	▪ CCP is FDA-approved for the treatment of COVID-19 in immunocompromised patients ▪ CCP, concomitantly dosed with RDV (5-10 days) or NRM/r, enhances viral clearance ▪ The response appears to be better early in the course of COVID-19 disease (≤7 days) May be considered for use in pregnancy

Alternative Agent

Tocilizumab (TCZ; Actemra)

JHHS recommends the treatment of:	Administration and duration:	Cautions and adverse effects:	Notes:
▪ Hospitalized patients receiving DEX 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	▪ 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**	▪ Exercise caution when co-administering TCZ with CYP3A4 substrate drugs when a decrease in effectiveness is undesirable. The most common adverse effects include constipation, anxiety, diarrhea, insomnia, hypertension, and nausea	▪ FDA EUA authorized for COVID-19 ▪ May be considered for use in pregnancy ▪ Patients with evidence of clinical progression of COVID-19 are most likely to benefit from this treatment. **JHMI requirements:** ▪ Non-formulary drug approval required ▪ CRP >7.5 required for immunocompetent patients ▪ Elevated CRP is not required for immunocompromised patients

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CCP, COVID-19 convalescent plasma; 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. Must also be ≤21 days since COVID-19 symptoms OR, if ≥21 days, evidence of ongoing SARS-CoV-2 replication.

b. **For highly immunosuppressed patients who have protracted COVID-19 disease, clinicians should:**
   - Consult with the JHH Transplant and Oncology Infectious Diseases teams (or ID consultants at other hospitals) regarding clinical decision-making

Table 2: Preferred and Alternative Pharmacologic Agents for Inpatient Treatment of Severe COVID-19 in Adults
· 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 in Highly Immunosuppressed 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.[1,2,11-15]

"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 evidence of ongoing viral replication based on RT-PCR from respiratory samples.[12,16,17] Persistent, stable, or increasing amplification of viral nucleic acid may suggest ongoing viral replication.[12,16,17] Viral positivity between days 10 and 21 may be consistent with acute COVID-19 in highly immunocompromised individuals. Protracted COVID-19 is analogous to protracted disease that can occur with other viruses (e.g., influenza, norovirus, respiratory syncytial virus) in patients with significant immunodeficiency.[18,19]

Treatment with antiviral medications, such as RDV, may change the course of protracted COVID-19 disease. Case reports of extended courses of RDV,[12,13] have reported clinical improvement and a reduction in viral nucleic acid from respiratory specimens during RDV administration.

To enhance viral clearance and prevent 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 feasible) plus high-titer convalescent plasma for immunocompromised patients. The rationale is based on growing evidence in highly immunosuppressed patients that resistance to SARS-CoV-2 protease inhibitors may develop, and that viral replication may persist 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.[20,21]

Obtaining a quantitative SARS-CoV-2 assay: JHMI does not perform testing in-house. The commercially available quantitative real-time RT-PCR test from Eurofins Viracor can be requested from JHH Pathology Customer Service, with results usually available within 1 week.

Treatment: Consult with JHH Transplant and Oncology ID (or ID consultants at other hospitals) regarding clinical decision-making. Combination antiviral therapy is preferred for patients with protracted COVID-19 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 COVID-19 convalescent plasma and COVID-19 convalescent plasma alone. Combination antiviral therapy has also been used with favorable outcomes reported in case series, sometimes with courses longer than the recommended 5-day course of NRM/r or molnupiravir.[22-28]

- **Hospitalized patients:** 2 to 3 units of convalescent plasma plus 10 days of RDV plus 5 days of NRM/r or 5 days of molnupiravir (molnupiravir is generally preferred because it has fewer drug-drug interactions than NRM/r; 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.

D. COVID-19 *Prevention* in Immunocompromised Patients

Pemivibart (Pemgarda) is a long-acting monoclonal antibody targeting the spike protein and inhibiting attachment of SARS-CoV-2. The FDA authorized an EUA in March 2024 for pre-exposure prophylaxis in high-risk individuals (aged 12 years and older, who are moderately to severely immunocompromised). Approval was based on an immunobridging study and an exploratory clinical trial. The risk of PCR-confirmed symptomatic COVID-19 was 94% lower (95% CI: 50%,99%) in the pemivibart arm.[29] This monoclonal targets a conserved region of the spike protein; hence, it has maintained neutralizing activity against most variants that have emerged as of September 2025.[30] Use of this monoclonal is authorized only when the national prevalence of variants with substantially reduced susceptibility to it remains ≤90%.

Pemivibart is not authorized for treatment or post-exposure prophylaxis of COVID-19. It may be particularly helpful for patients who are highly immunosuppressed and/or B-cell-depleted and are not expected to mount a robust response to SARS-CoV-2 vaccines. The standard dose of pemivibart is 4,500 mg for initial and repeat doses administered every 3 months by IV infusion over a minimum of 60 minutes. After infusion, recipients must be monitored for 2 hours (~3 hours total).

Anaphylaxis occurred among 0.6% (4/623) of clinical trial participants during both the first and the second infusion, but this effect has not been as common during real-world use.

Pemivibart is currently unavailable per JHHS formulary and cannot be ordered. It is available at a number of free-standing infusion centers. Providers or patients can contact Invivyd to arrange for infusions via For US Healthcare Professionals | Invivyd Care.

IV. Summary of Key Clinical Trial Evidence for Preferred and Alternative Agents

FDA-approved medications for the treatment of COVID-19 include remdesivir (RDV; Veklury), nirmatrelvir/ritonavir (NRM/r; Paxlovid), and baricitinib (BAR; Olumiant, FDA approval for COVID). Tocilizumab (TCZ; Actemra) and anakinra (Kineret) are FDA-approved for other indications and have EUAs for the treatment of COVID-19. Non-FDA-approved medications available through FDA EUAs for COVID include molnupiravir (Lagevrio) and vilobelimab (Gohibic). DEX does not have a specific FDA indication for COVID-19, but it has become a standard treatment for severe cases of the disease. Monoclonal antibodies for the treatment of COVID-19 are no longer available because they are not effective against the currently circulating strains of SARS-CoV-2. See: FDA > Coronavirus (COVID-19) Drugs.

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

A. Preferred Agents

Remdesivir (RDV; Veklury)

- **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).[31] 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[32] 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, unlike the ACTT-1 study. It is unclear why no benefit was observed in this study in contrast to the reduced time to recovery and the 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.[33] 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.[34] The PINETREE population no longer reflects the current epidemiology, where nearly all immunocompetent adults have either been exposed or vaccinated and have anti-SARS-CoV-2 antibodies.

- Its original intent to abort serious infection was based upon 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%) experienced a COVID-19-related hospitalization, compared with 15 (5.3%) in the placebo arm (P = .008), resulting in a relative risk reduction of 87%. There were no deaths in either arm. Adverse events were similar in both arms.

Nirmatrelvir/Ritonavir (NRM/r; 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 NRM/r or placebo.[35] 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 NRM arm reached the primary endpoint, compared with 66 (6.3%) in the placebo arm (relative risk reduction, 88%; P = 0.001). No deaths occurred in the NRM arm, and 12 occurred in the placebo arm. Adverse events were overall lower in the NRM arm. For healthy, standard-risk individuals, the EPIC-SR RCT did not reveal significant differences in signs and symptoms between those who received NRM/r and those who received placebo.
- NRM/r has not demonstrated efficacy when used for post-exposure prophylaxis.[36] A double-blind clinical trial assessed symptomatic COVID-19 14 days after exposure to a household contact in participants who received 5 or 10 days of NRM/r (921 and 917 participants, respectively) or placebo (898 participants). Treatment was initiated in all within 96 hours of randomization. Symptomatic COVID-19 occurred among 2.6% (5-day arm), 2.4% (10-day arm), and 3.9% (placebo arm). There was no statistically significant difference between the groups.

Baricitinib (BAR; Olumiant)

Early in the COVID-19 pandemic, observational and clinical trial data suggested that treatment with TCZ, combined with a steroid, could improve patient outcomes. Data now suggest at least equal benefit from BAR with and without concomitant steroids. In response to early experience with TCZ and the lack of a head-to-head comparison between TCZ and BAR, this writing group initially preferred TCZ over BAR. This group has now changed its recommendation to prefer BAR given that: (1) the FDA has added COVID-19 as an approved indication for BAR (but not TCZ); (2) clinical trials of BAR, with and without concomitant steroids, have consistently demonstrated reduced mortality; and (3) BAR has fewer adverse effects than TCZ, which remains under emergency use authorization and is now recommended as an alternative agent.

- **ACTT-2:** This study, which compared BAR and RDV with placebo and RDV, reported a statistically significant difference in the primary outcome of time to recovery. Participants in the BAR arm reached hospital discharge 1 day earlier than those in the placebo arm.[37] The ACTT-4 study compared BAR with DEX among individuals receiving RDV. The study was halted after enrolling 1,010 participants because the likelihood of identifying a difference between arms was low. Participants were enrolled in low-flow oxygen, high-flow oxygen, or non-invasive mechanical ventilation; 75% received DEX before enrollment (1 dose was allowed). Mechanical ventilation-free survival by day 29 was 87% in the BAR plus RDV arm and 87.6% in the DEX plus RDV arm.[38]
- **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 BAR or placebo; 96% received corticosteroids and 19% received RDV.[39] The primary outcome of progression to high-flow oxygen, non-invasive ventilation, invasive ventilation, ECMO, or death by day 28 was not significantly different between groups (27.8% for BAR vs. 30.5% for placebo; P=.2). All-cause mortality, a secondary outcome, was lower in the BAR group (8.1% for BAR vs. 13.1% for placebo; P=.002).

  The COV-BARRIER study evaluated the use of BAR in critically ill hospitalized patients who received mechanical ventilation or ECMO and had elevated inflammatory markers.[40] In this subgroup, 101 participants were randomized to receive BAR 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 BAR group died, compared with 29 of 50 participants (58%) in the placebo group (HR, 0.54; P = .03). This difference was also maintained at 60-day mortality.
- **RECOVERY:** Between February and December 2021, the open-label, multi-arm RECOVERY trial randomized participants to receive BAR (n = 4,149) or usual care (n = 4,008); 96% of participants received corticosteroids.[41] 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 BAR and 14% who received usual care (age-adjusted rate ratio, 0.87; P=0.0026).

- **Meta-analysis and other studies:** A review of individual participant data (12,902) from 12 studies of JAK inhibitors (7 with BAR, 3 with tofacitinib, 2 with ruxolitinib) conducted from 2020 to 2022[42] found decreased all-cause mortality, with an adjusted odds ratio of 0.67 associated with the use of a JAK inhibitor. In subgroup analysis, a benefit or a trend toward benefit was observed with or without the addition of DEX or TCZ. The review also found a probable decreased risk of severe adverse events in those who received JAK inhibitors.
- A retrospective analysis of outcomes and adverse effects, which included 956 participants from 11 hospitals in the state of Georgia (U.S.) who received either TCZ or BAR, found no differences in mortality following propensity-score matching.[43] However, adverse effects were significantly higher in the TCZ group compared with the BAR group: secondary infections (32% vs 22%; $p < 0.01$); thrombotic events (24% vs 16%; $p < 0.01$); and acute liver injury (8% vs 3%; $p < 0.01$). These two studies suggest fewer adverse outcomes and lower mortality with BAR.

Dexamethasone (DEX; multiple trade names)

Systemic corticosteroids:

- **RECOVERY:** The RECOVERY trial, an unblinded open-label, multi-site, multi-arm RCT conducted in the United Kingdom, included a DEX treatment arm. All patients hospitalized with COVID-19 were eligible to participate in the study.[44] The 2,104 participants randomized to the DEX 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 non-invasive 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 DEX 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=0.0003) for participants on mechanical ventilation, 0.8 (P=.002) for those receiving non-invasive 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 DEX treatment.

  RECOVERY trial findings may not be generalizable to corticosteroid use overall for the treatment of COVID-19. DEX 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, DEX 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 included 86 participants in the analysis and compared results in the group prescribed a glucocorticoid (methylprednisolone) with a group randomized to receive either a glucocorticoid or no glucocorticoid.[45] 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 non-invasive 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.[46] 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.[47] 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 across all assessed

subgroups: with or without mechanical ventilation, age (≤ or >60 years), sex, and duration of symptoms (≤ or >7 days). There was no apparent difference between the use of DEX 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.[48] 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*=0.004). 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.[49] The composite primary endpoint was the 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).

COVID-19 Convalescent Plasma (CCP) 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.[50-55] 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.[56] 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.[57] 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).

Expanded access program (EAP) studies in hospitalized participants: Analyses of convalescent plasma administered through the open-label FDA EAP indicated overall relative safety (although not compared with placebo) and suggested reduced mortality with transfusion soon after diagnosis (≤3 days) in those already hospitalized; 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.[58] 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.[58] 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).[59]
- A large retrospective study from HCA Healthcare included 4,337 participants who received convalescent plasma and 8,708 who did not. The study reported lower mortality in those who received convalescent plasma (hazard ratio, 0.71; P < .001). A difference in mortality was observed for those who received convalescent plasma within 3 days of hospital admission but not among those who received it 4 to 7 days after admission.[60]

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*).[61] 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.[62] 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.[63]
- A multicenter, Phase 3, open-label trial conducted in Europe during the Omicron era among clinically vulnerable patients with mild COVID found that the 59 immunocompromised outpatients who received CCP within 4 days of symptom onset had no hospitalizations or deaths. Among the 58 participants in the standard-of-care arm, there were 5 hospitalizations and 1 death [absolute difference −8.6%; 95% CI, −19% to −0.80%; *P* = 0.027].[64]

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[56,57]).

Risks: The risks associated with the use of convalescent plasma include a very low risk of pathogen transmission (~1 in 2 million units),[65-67] allergic transfusion reactions, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI), all of which are rare.[66,67] 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%.[68] 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,[69] 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 the safety of convalescent plasma therapy but not for its efficacy in patients with severe COVID-19.

OneBlood and Stanford Blood Center are FDA-approved COVID-19 convalescent plasma with high-titer SARS-CoV-2 antibodies: In December 2024, based on prior RCT data, the FDA approved OneBlood CCP and in October 2025, Stanford Blood Center for use in COVID-19 treatment in immunosuppressed patients who are not expected to mount antibody-sufficient responses to the virus or vaccine.

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.[70] 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 the placebo arm participants were hospitalized or died (RR, 31%; 95% CI, 0.48–1.01). Adverse events were similar in both arms.

Tocilizumab (TCZ; Actemra)

The lack of head-to-head trials with other immunomodulators and population differences between studies make it challenging to rank the relative efficacy of TCZ, BAR, and anakinra.

In the EMPACTA,[71] REMAP-CAP,[72] and RECOVERY[73] studies of TCZ (see below), in which most participants received corticosteroids, all reported improvement in the primary outcome with TCZ. Earlier TCZ studies that did not include participants treated with corticosteroids failed to observe a difference in the primary outcome between TCZ and the comparator arm. BAR reduced recovery time compared with placebo in the ACTT-2 study, primarily among participants receiving high-flow oxygen or non-invasive ventilation.[74] All participants received RDV; no data on corticosteroids were provided. The ACTT-4 study compared DEX with BAR, 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 BAR study, in which most participants received corticosteroids but <20% received RDV, reported reduced mortality as a secondary endpoint.[40] 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.[75]

See baricitinib discussion for why baricitinib is now favored (2025) compared to tocilizumab for progressive, severe COVID-19 pneumonia.

TCZ 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 TCZ or placebo found no difference in clinical worsening or death at day 14 and day 28 endpoints.[76]
- 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[77] or clinical progression at 14 days[78]; 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 TCZ than those who received a placebo (9% and 35%, respectively).[79]
- Roche announced that an RCT, which included 450 participants with COVID-19 pneumonia and SpO2 <94%, found no significant difference in clinical status or mortality but reported a significantly shorter time to discharge among those who received TCZ (20 days vs. 28 days).[80,81]

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

- **EMPACTA:** The Roche EMPACTA study of TCZ reported a reduction in mechanical ventilation in a double-blind RCT of 389 participants with COVID-19 pneumonia.[82] The hazard ratio of the primary outcome of progression to mechanical ventilation or death was 0.56 (*P*=.04) among those randomized to the TCZ 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 TCZ 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.[83,84]
- **REMAP-CAP:** This international adaptive clinical trial platform tested multiple COVID-19 therapeutics and examined TCZ or sarilumab compared with standard care.[72] Participants were adults with COVID-19 admitted to an ICU who received respiratory or cardiovascular support through high-flow oxygen, non-invasive or invasive mechanical ventilation, or pressor drug therapies (19%); 77% received a corticosteroid. The median organ support–free days within 21 days of randomization were 10 days for TCZ and 0 days for standard care. Hospital mortality was 28% in the TCZ 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 TCZ treatment arm.[73] Participants were first randomized to one of the following: usual care, DEX, LPV/RTV, HCQ, azithromycin, or colchicine. Participants were subsequently considered for randomization to TCZ or no TCZ 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 TCZ or no TCZ. Of these, 55% received high-flow oxygen or invasive or non-invasive mechanical ventilation, and 45% received supplemental oxygen via nasal cannula. The primary endpoint of 28-day mortality occurred among 29% of the TCZ group and 33% of the no-TCZ group (*P*=0.007). In subgroup analysis, TCZ 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 TCZ or standard care.[23] 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 TCZ 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 TCZ arm because mortality at

day 15 occurred in 11 (17%) of TCZ recipients and only 2 (3%) of the standard-of-care/placebo group (OR, 6.42; 95% CI, 1.59–43.2).

Anakinra (Kineret)

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; TCZ 0.78-0.89; BAR 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 TCZ, BAR, and anakinra.

- A retrospective cohort study from Italy reported that 3 of 29 patients (10%) who received anakinra died, compared with 7 of 16 patients (44%) who did not receive anakinra.[85]
- The SAVE non-randomized study[86] 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 DEX, and 74% received RDV. At day 28, 50.4% of participants in the anakinra group and 26.5% of those in the placebo group had achieved full recovery. 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.

Metformin

- While some early data suggested benefit, the evidence does not favor use of metformin for routine care of people with COVID-19 or post-COVID-19 symptoms. This guideline document does not recommend its use outside of a clinical trial.
- In the ACTIV-6 trial, metformin did not shorten time to sustained recovery or symptom resolution among ambulatory patients. Among the 2991 participants randomized to metformin or placebo, there was no difference in time to symptom resolution, hospitalization, or death. A systematic review and meta-analysis also did not support use for acute infection.[88]
- COVID-OUT was a multi-arm RCT of ambulatory patients aged 30 to 85 years old, who were obese and had less than 7 days of symptoms. The primary endpoint of hypoxemia, emergency department visit, hospitalization, or death. This study reported no significant difference in outcomes between metformin and placebo (or any of the other agents).[91] For the secondary endpoint of symptom reduction at 90 days, the trial favored metformin.[89] 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. Post-acute COVID-19 symptoms were subsequently assessed in the COVID-OUT study. Of the 1,126 participants with long-term follow-up, 93 (8.3%) had a diagnosis of post-COVID-19 syndrome by 9 months. The incidence differed by metformin receipt: 6.3% of participants who received metformin and 10.4% of those who received placebo were diagnosed with post-COVID-19 syndrome ($p = 0.01$). In subgroup analysis, metformin appeared to be most effective in participants <45 years old, those with a BMI ≥30, and those initiated within 3 days of symptom onset.[90]
- Another trial, the TOGETHER trial, was withdrawn due to errors in data analysis regarding the primary outcome, which led to an inappropriate and premature halt in this adaptive trial.[87] Therefore, in November 2025, the editor of Lancet Regional Health – Americas retracted this paper.

V. Development of This Guideline

Box 3: COVID-19 Pharmacologic Treatment Guidance Writing Group

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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 the 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 is invited to provide comments to C19Workgrp@jhu.edu.

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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,

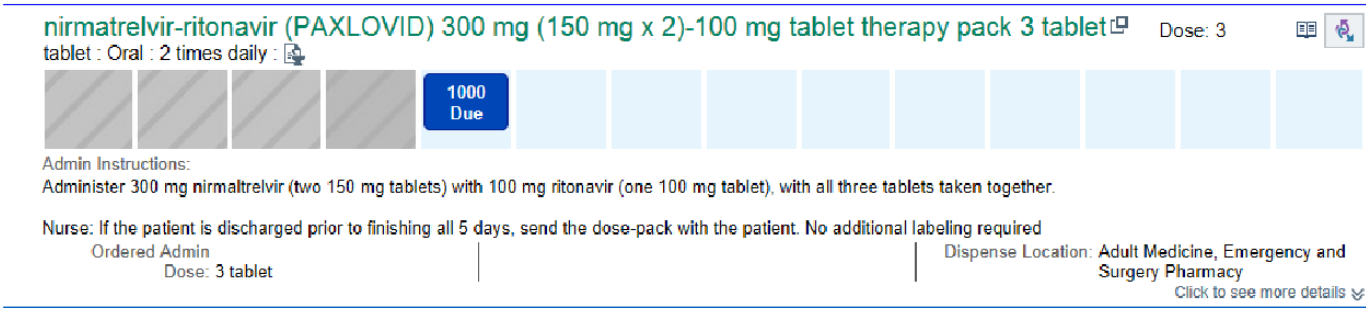
On November 30th, 2022, the FDA revoked the emergency use authorization (EUA) for bebtelovimab. As a result of that decision, Paxlovid (nirmatrelvir/ritonavir) was added to the JHHS Formulary. Hospitalized patients with symptomatic mild-to-moderate COVID-19, who were not hospitalized due to COVID-19,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

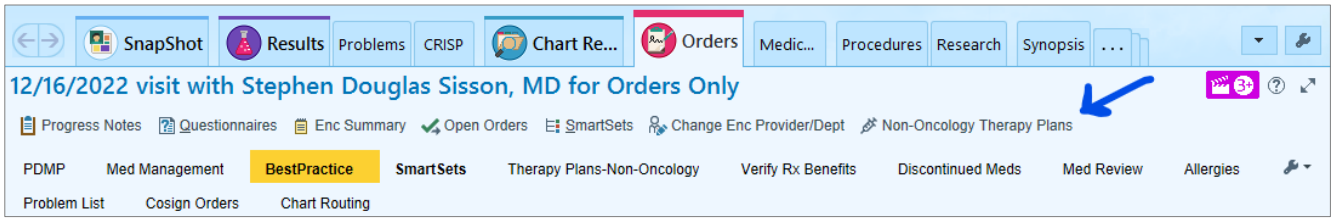
Introduction

- 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 patients who cannot tolerate Paxlovid **and** are within 7 days of the onset of symptoms **and** are at risk for progression to severe disease, prescribe 5 days of remdesivir (typically immunocompromised patients).
- 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.

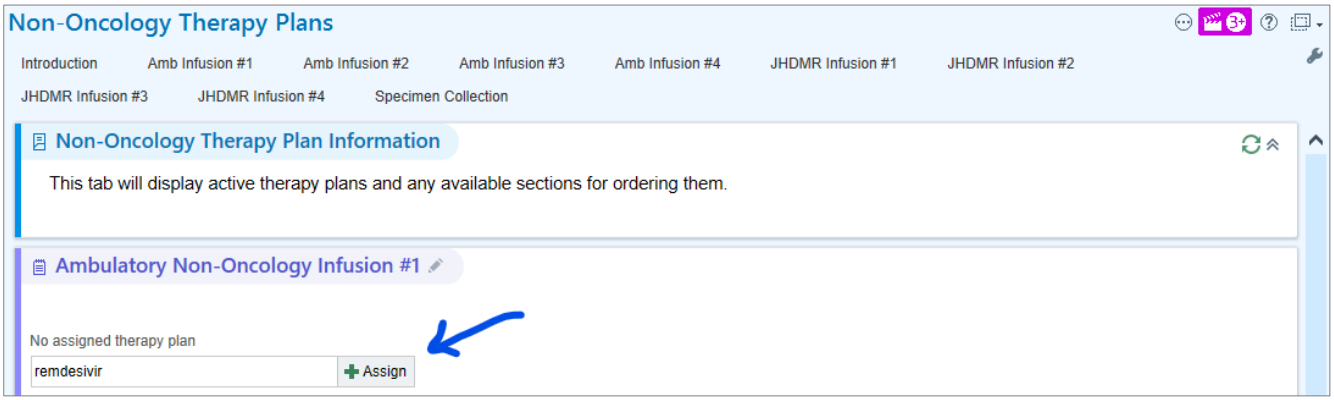
Ordering Instructions

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**.

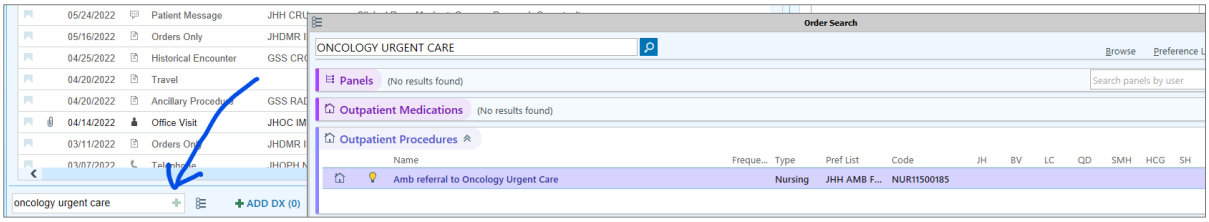


3. Once the therapy plan is submitted, send a simultaneous email to adultivinfusion@jhmi.edu to alert them to the patient. The Park Infusion team will reach out to the patient to schedule and provide instructions to the patient.

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.

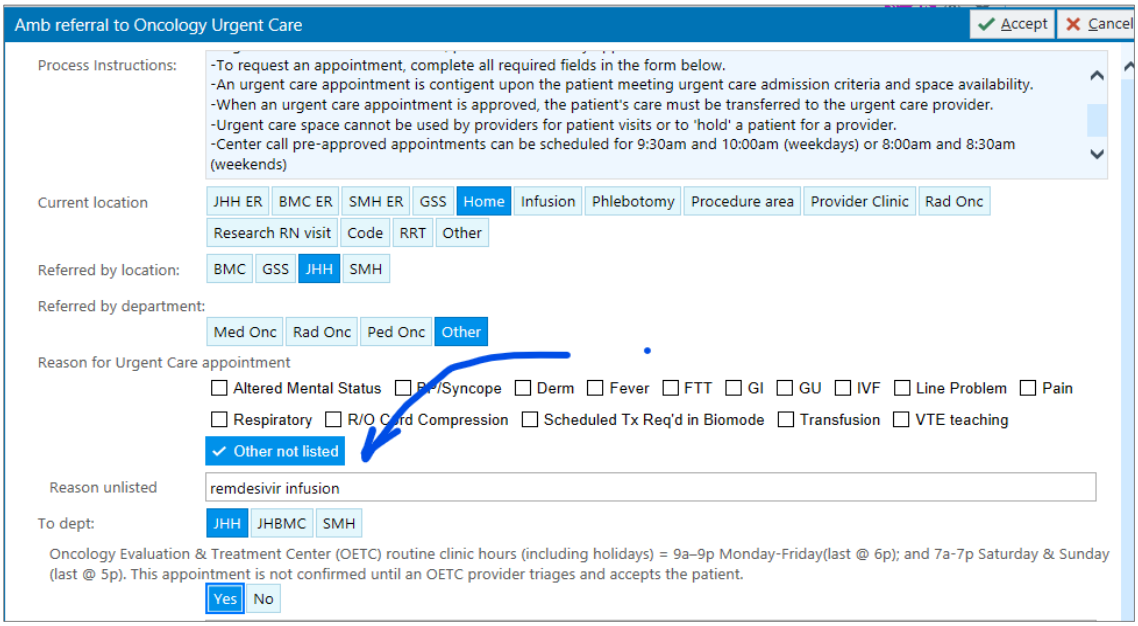
5. If the 5-day infusion course includes a weekend or holiday, you will need to refer the patient to Oncology Urgent Care as described below. Oncology will assume care of the referred patient on weekends and holidays.

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 5-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.