Management of Inpatient and Outpatient COVID-19: Guidance for Fred Hutch Cancer Center Providers

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This document is to provide guidance regarding SARS-CoV-2 infections in Fred Hutch patients. Recommendations differ from the UW Treatment Guidelines in several situations, including:

- Mild/ moderate infection in Heme malignancy, HCT/ IEC therapy, anti-CD20 therapy patients
- Patients with asymptomatic infection (including those with impending and significant immunosuppression)
- Immunocompromised patients with persistent symptomatic infection

This document is meant to be used as guidance, and in conjunction with clinical reasoning.

Figure 1: Pathway for Determining Management Strategy for Fred Hutch Patients with a SARS-CoV-2 Positive Test

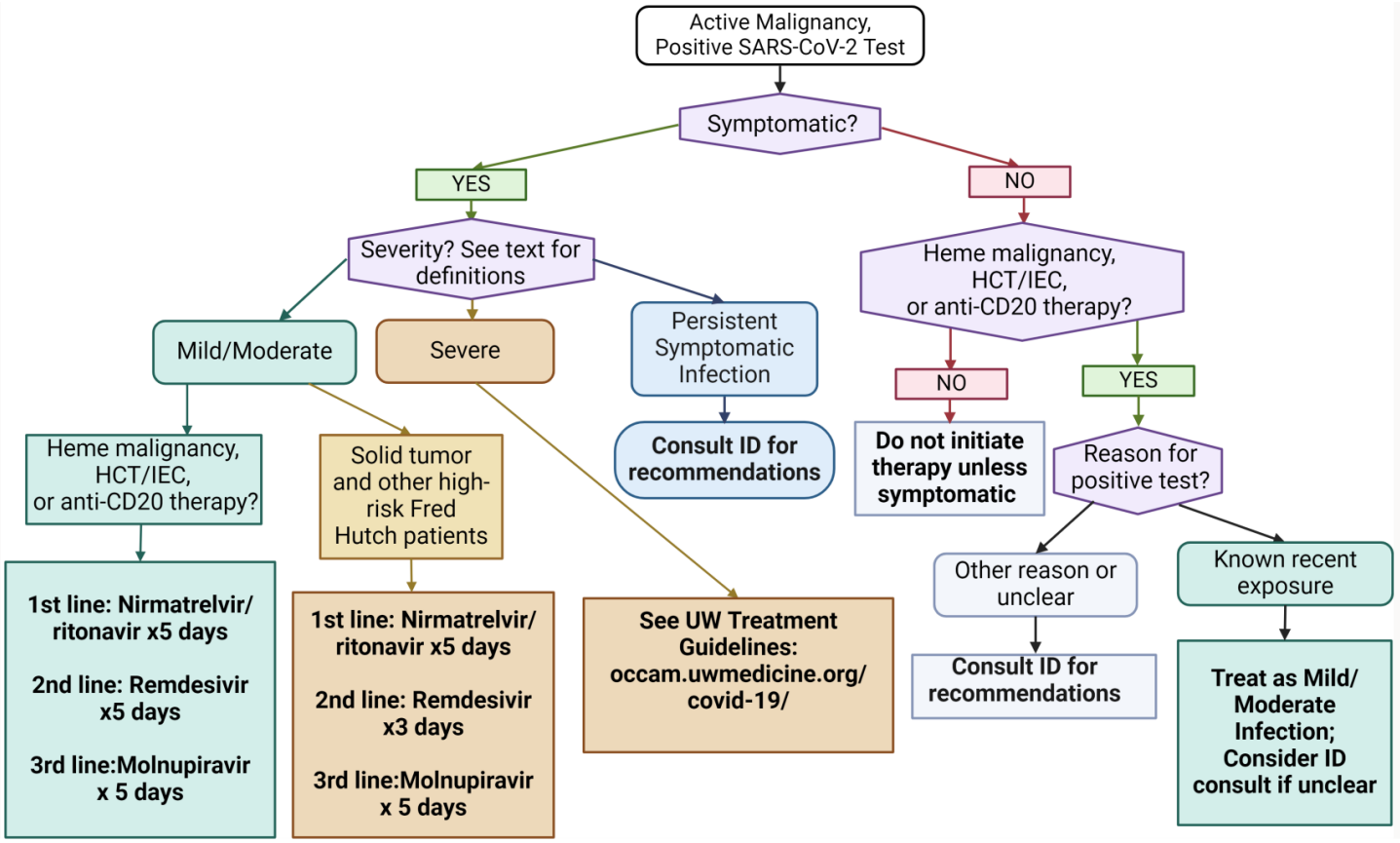

Table 1: Management of Mild/Moderate COVID-19

	1st Line	2nd Line*	3rd Line
Heme malignancy, HCT/IEC therapy, anti-CD20 therapy	Nirmatrelvir/ritonavir x 5 days**	Remdesivir x 5 days Fred Hutch Provider Resources	Molnupiravir*** x 5 days; Consider ID Consult
Solid tumor and other high-risk Fred Hutch patients	Nirmatrelvir/ritonavir x 5 days**	Remdesivir x 3 days	Molnupiravir*** x 5 days; Consider ID consult

**If unable to give nirmatrelvir/ritonavir due to significant drug-drug interactions, severe hepatic, renal impairment (eGFR < 30 mL/ min)*

*** When considering durations longer than 5 days, ID should be consulted for guidance (eg. Persistent COVID-19 Infection)*

****Molnupiravir is offered under EUA criteria: FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES (fda.gov)*

Rationale for Mild/Moderate Treatment Recommendations

- Nirmatrelvir/ritonavir is preferred for mild/moderate COVID-19 for several reasons: it is consistent with NIH treatment guidelines, daily cost is less than a remdesivir course, efficacy is considered similar to remdesivir, and nirmatrelvir/ritonavir is easier to transition from inpatient to outpatient given its oral formulation.
- It is unclear whether a 3-day course of remdesivir (as was studied in the PINETREE study[1]) will adequately reduce disease progression in severely immunocompromised patients. Remdesivir was studied for up to 10 days in hospitalized patients and appears relatively safe.[2] In the highly immunosuppressed category (Heme malignancy, HCT/IEC therapy, anti-CD20 therapy), a duration of 5 days is recommended, acknowledging degree of immunosuppression and being cognizant of logistical concerns. Internal data, including patients treated with nirmatrelvir/ritonavir, currently supports a duration of 5 days for this patient population.

IV remdesivir administration alone is not a reason to prolong hospitalization in patients admitted for reasons other than COVID-19. Remdesivir is available in the outpatient setting with a limited number of infusion spots dedicated each week.

Severe COVID-19

- Treat as per UW COVID-19 Treatment recommendations (https://occam.uwmedicine.org/covid-19-reference-kit/ OCCAM is also accessible via hyperlinks in the EPIC toolbar)
- Combination therapy may be considered on a case-by-case basis, in conjunction with ID consultation

Asymptomatic Infection

Occasionally, asymptomatic patients will test positive for SARS COV-2. A detailed patient history is important to delineate between pre-symptomatic infection, resolving infection or false positive test. See COVID-19 definitions at end of document. For suspected pre-symptomatic infection (see page 3), the patient can be closely monitored and treatment initiated for mild/moderate infection as soon as symptoms manifest. However, for pre-symptomatic high-risk patients (Heme malignancy, HCT/IEC, anti-CD20 therapy) consider initiation of treatment as mild/moderate infection. ID consultation is recommended in cases of suspected resolving infection, or if the classification of the asymptomatic infection is unclear.

Persistent Lower Tract COVID-19 Infection

Prolonged, persistent or relapsing COVID-19 is characterized by long-term, lower respiratory tract SARS-CoV-2 infection with or without concurrent hyperinflammatory responses. Patients may require intermittent or long-term supplemental oxygen. Management of this infection is challenging as all large, randomized control studies for COVID-19 therapeutics have primarily focused on newly diagnosed infections. Therefore, ID consultation is recommended when this scenario is encountered.

When to suspect relapsed/refractory lower respiratory tract infection:

- Initial PCR positive > 28 days prior and low suspicion for re-infection based on epidemiologic history and pattern of test results
- Persistent upper and/or lower tract PCR positivity. Consider bronchoscopy to evaluate for SARS-CoV-2 PCR, and alternative diagnoses, in patients with negative upper tract PCR
- Persistent chest CT findings consistent with SARS CoV-2 infection
- Ongoing or worsening pulmonary symptoms
- B-cell depletion (risk factor best described in the literature)[3-8]
    - Treatment for lymphocytic malignancies (ALL, CLL, lymphomas)
    - Anti-CD20 monoclonal antibodies
    - CD19- directed CAR-T cell therapy
- Other highly immunocompromised populations, including recent HCT or SOT recipients and patients with hematologic malignancies may also be at risk

Definitions and Categories of SARS-CoV-2 Infection

Asymptomatic infection: SARS-CoV-2 infection detected on a screening test with no symptoms of COVID-19. Asymptomatic infection may represent one of the scenarios included below. A careful history and repeat PCR to follow the trajectory of Ct values may be helpful to distinguish between these possibilities. For situations other than pre-symptomatic infection, ID consultation is recommended so that they may review the case in detail, acquire the CT values and provide guidance on further diagnostics and potential treatment.

- Pre-symptomatic infection: The patient was recently infected and has not yet developed symptoms. Recent negative SARS-CoV-2 tests and/or a history of a recent high-risk exposure may indicate pre-symptomatic infection.
    - If the patient becomes symptomatic, consider treatment.

- Resolving infection: History of a prior infection, remote onset of symptoms with a trajectory of clinical improvement. Patients with resolving infection may be less likely to benefit from SARS-CoV-2 therapeutics, but Infectious Diseases will consider clinical symptoms, duration of viral shedding, and potential for recrudescent infection in the setting of increased immunosuppression /chemotherapy when making treatment decisions.

- False positive result: A very high Ct value may be a false positive result. A negative repeat PCR within 72 hours supports a false positive result.

Mild/moderate infection : Patients with mild illness may exhibit a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell. Moderate illness is defined as evidence of lower respiratory disease by symptoms (SOB) or imaging, with SpO_2 ≥94% on room air.

Severe/critical infection: Patients with COVID-19 are considered to have severe illness if they have SpO_2 <94% on room air and/or PaO_2/FiO_2 <300 mm Hg, RR >30, or lung infiltrates >50%. Patients with severe illness may develop shock or end-organ dysfunction and require ICU level care.

Persistent infection: Evolving term used to describe patients with a remote diagnosis of SARS-CoV-2 infection (>28 days prior) which may have improved initially, but who have recurrent, persistent, or progressive respiratory symptoms. This pattern of illness has been seen in immunocompromised patients, particularly patients being treated for B-cell malignancies and patients who have received anti-CD20 and other lymphodepleting therapies.[96] Some patients may have been treated with therapeutics in the past. Upper respiratory tract PCR may be negative, but lower tract PCR will be positive and imaging shows lung parenchymal changes characteristic of COVID-19. Patients may have mild, moderate, severe, or critical illness (or fluctuate between). Treatment of patients with prolonged, persistent, or relapsing infection requires careful consideration. This scenario infection should be differentiated from re-infection whenever possible. For example, a remote history of SARS-CoV-2 (> 90 days prior), followed by documented negative PCR testing and/or a history of recent exposure may indicate re-infection. Consultation with the Virology lab for sequencing may be helpful to distinguish between prolonged/persistent/relapsing infection and re-infection. Prolonged/persistent/relapsing infection is distinct from “long COVID” or post-acute sequelae of SARS-CoV-2 infection (PASC).

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