

INTERIM GUIDELINES FOR COVID-19 MANAGEMENT IN HEMATOPOIETIC CELL TRANSPLANT AND CELLULAR THERAPY PATIENTS

Version 1.2
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Summary of significant changes since Version 1.1:

1. Removed specific guidance around travel-related exposure risk for recipients and donors.
2. New section (IV) with additional treatment considerations, including specific therapies.

I. SCOPE

This document is intended as a guide for diagnosis and management of COVID-19 (caused by the virus SARS-CoV-2) in adult and pediatric hematopoietic cell transplant (HCT) and cellular therapy patients. There is currently limited data on the epidemiology and clinical manifestations of COVID-19 in this population¹. Given the experience with other respiratory viruses, we anticipate patients may develop severe clinical disease and thus provide the following general principles for cancer centers across the nation. Specific practices may vary depending on local epidemiology and testing capacity. These guidelines will be modified as new information becomes available, including more data on epidemiology and clinical outcomes, and efficacy of drug therapies including clinical trial outcomes of novel therapeutics.

This document will **not cover specific infection prevention policies and procedures**; local and institutional guidelines should be followed. In the setting of known high community prevalence of COVID-19, clinic visits that are not critical should be either deferred or substituted with telemedicine visits if deemed appropriate and feasible.

II. DIAGNOSTIC CONSIDERATIONS IN HCT AND CELLULAR THERAPY PATIENTS

In the setting of known high community prevalence of COVID-19 or exposure to a known case of COVID-19, the following evaluations should be performed. If testing not available, risk should be ascertained based on local epidemiology.

- A. In any patient with upper or lower respiratory symptoms, send PCR testing for SARS-CoV-2 *in addition* to other respiratory virus PCR testing from any respiratory sample obtained.
 - Follow CDC recommendations for swab collection (<https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>).
 - Nasal sampling should be preferentially performed over oral sampling given preliminary data suggesting higher viral loads in nasal samples².
 - Nasal wash is discouraged; however, centers that use this method or if availability of swabs becomes scarce, washes could be done with appropriate personal protective equipment as per guidelines.
- B. In patients positive for SARS-CoV-2 in an upper respiratory tract sample, chest imaging should be considered.
- C. Patients without SARS-CoV-2 detected in the upper respiratory tract but with clinical symptoms of lower respiratory tract infection (LRTI; shortness of breath, hypoxia, tachypnea), chest imaging to evaluate for lower respiratory tract infection should be considered.
 - Preliminary reports suggest the possibility of discrepancy between upper and lower tract specimen positivity³, as has been seen with other respiratory viruses⁴.
- D. Routine bronchoalveolar lavage (BAL) is not recommended if a patient tests positive for SARS-CoV-2 given risk of transmission amongst health care workers, unless a co-infection is suspected. If chest imaging is abnormal and in patients for whom it is clinically indicated (e.g., those receiving invasive mechanical ventilation), a lower respiratory tract endotracheal tube aspirate or BAL sample should be collected and tested for SARS-CoV-2. Co-pathogens should be evaluated and treated.

- E. See testing recommendations below for HCT and cellular immunotherapy candidates and donors (section III).

III. CONSIDERATIONS FOR EVALUATION PRIOR TO HCT OR CELLULAR THERAPY *(Adapted from EBMT guidelines published 3/16/2020)⁵*

Though there is limited data regarding the impact of COVID-19 in transplant candidate and donors and cellular therapy recipients, there is sufficient concern that COVID-19 could have a significant impact on posttransplant or post therapy outcomes. The following recommendations should be considered while weighing the risk of delaying or altering therapy plans with the risk of progression of underlying disease.

A. HCT and Cellular Therapy Candidates:

- a. In HCT and cellular therapy candidates with symptoms of an acute respiratory tract infection, patients should be tested for respiratory viruses preferably by multiplex PCR, including SARS-CoV-2 if available. If testing is not available, procedures including PBSC mobilization, BM harvest, T cell collections and conditioning/lymphodepletion should be deferred for a minimum of 14 days and symptoms have resolved. Since the sensitivity of the assay is not clearly defined, deferral could be considered even with a negative PCR by weighing risks of underlying disease progression.
- b. If SARS-CoV-2 is detected in a respiratory specimen, HCT or cellular therapy procedures should be deferred. In patients with high risk underlying malignancies, procedures including PBSC mobilization, BM harvest, T cell collections and conditioning/lymphodepletion should be deferred until the patient is asymptomatic and has at least two consecutive negative PCR tests each approximately one week apart (deferral for 14 days minimum), if available. If possible, a conditioning regimen with the least intensity should be used.
- c. In HCT and cellular therapy candidates with close contact with a person infected with SARS-CoV-2, procedures including PBSC mobilization, BM harvest, T cell collections and conditioning/lymphodepletion should not be performed for at least 14 days and preferably 21 days from the day of last contact. Affected patients should be closely monitored for the development of infection, with two consecutive negative PCR tests each approximately one week apart (deferral for 14 days minimum), if available.
- d. HCT and cellular therapy candidates should refrain from non-essential travel.
- e. If prevalence of COVID-19 is thought to be high in the community, all HCT and cellular therapy candidates should undergo screening for SARS-COV-2 infection by PCR in respiratory specimens at the time of initial evaluation and 2 days prior to conditioning/lymphodepletion, regardless of the presence of symptoms, if testing is available.
- f. If prevalence of COVID-19 is thought to be high in the community, for certain conditions, interim treatment and/or longer deferral of definite therapy should be considered when feasible (for example, multiple myeloma, germ cell tumors, consolidative transplants).

B. HCT Donors:

SARS-CoV and MERS-CoV have been detected in blood, although there have not been any reports of transmission from donor to recipient either in transfusion of blood products or cellular therapies⁶. Early reports have demonstrated SARS-CoV-2 can also be detected in blood, but no information is available on the kinetics of blood detection and whether it is related to disease severity⁷. Current American Association of Blood Banks guidelines do not recommend screening for SARS-CoV-2 in blood products⁸ and current Food and Drug Administration guidelines recommend considering the donor's infection and exposure history in the 28 days prior to donation⁹. Given uncertainty regarding the significance of detection in blood and current lack of testing capability, the following recommendations rely on donor infection and exposure history and testing in respiratory samples.

- a. In donors with SARS-CoV-2 detected in a respiratory sample, the donor is considered ineligible to donate. However, an ineligible donor may be collected in certain situations. Refer to facility standard of practice for circumstances for use and documentation of urgent medical need and appropriate counseling on risks and benefits. Otherwise, consider donor eligibility if no history of severe respiratory disease and 28 days have elapsed since symptom resolution and since SARS-CoV-2 PCR from respiratory sample has become negative.
- b. In donors with close contact with a person diagnosed with COVID-19, donor should be excluded from donation for at least 28 days. In individual circumstances, a donor may be considered eligible if respiratory samples are negative for SARS-CoV-2 by PCR and donor is asymptomatic. Donor should be closely monitored for COVID-19.
- c. Current recommendations for unrelated donors from the National Marrow Donor Program (NMDP) are as follows; please refer to NMDP guidelines for updated guidance.

“The NMDP strongly recommends cryopreservation of all donor products as far in advance of the initiation of patient conditioning as is feasible, dictated by the clinical situation of the patient. At this time, it is not possible to make specific recommendations as to the exact timing between collection and cryopreservation and initiation of conditioning. We believe at this time that the risk of viral transmission via bone marrow or PBSC donation to the recipient is very low. The U.S. Food and Drug Administration continues to report that there have been no reported or suspected cases of transfusion-transmitted COVID-19 to date. In addition, no cases of transfusion-transmission were ever reported for the other two coronaviruses that emerged during the past two decades (SARS, the Severe Acute Respiratory Syndrome Coronavirus, and MERS-CoV, which causes Mideast Respiratory Syndrome). There are augmented donor screening measures – which may include travel deferrals – already in place to prevent individuals with clinical respiratory infections or exposure history from donating bone marrow or PBSC products, ensuring the safety of the grafts we are supplying.

This recommendation is mainly based on the challenges in predicting whether an asymptomatic donor with no history of travel or exposure will become infected with SARS-CoV-2 in the interval between workup and day of planned bone marrow harvest or PBSC collection. Additionally, some donors are asked to be transported via air to that site of collection and may become concerned with their own safety related to travel.

Your case manager will be happy to work with you to make arrangements with the donor and donor center for cryopreservation.”

- d. If possible, ensure that an alternative stem cell source will be available. If multiple possible donors are available, choose a donor without risk.
- e. Donors within 28 days prior to donation should practice good hygiene and avoid crowded places and large group gatherings.

IV. TREATMENT CONSIDERATIONS FOR HCT AND CELLULAR THERAPY PATIENTS:

There are currently no specific therapies available for the treatment of patients with COVID-19. The following **interim** recommendations are meant to provide guidance for the management of adult and pediatric hematopoietic cell transplant (HCT) and cellular therapy patients. Recommendations are based on available data and experience from SARS-CoV, MERS-CoV, and in the current SARS-CoV-2 pandemic. Of note, little to no data is currently available on treatment in immunocompromised hosts, and even less data is available for pediatric patients. **These guidelines will be updated as new information becomes available, including information on new clinical trials.** In general, given the lack of convincing data on clinical efficacy, clinicians are encouraged to enroll patients into clinical trials in order to obtain data on the toxicity and efficacy of available and new agents.

Based on experience with other respiratory viruses, early therapy prior to development of lower respiratory tract infection may prevent severe outcome. No data is available for COVID-19. Data showing that SARS-CoV-2 viral load in upper respiratory specimens is highest at presentation and before symptoms of LRTI suggests that early antiviral therapy may be beneficial. Treatment considerations should be made based on the risk/benefit profile for each individual patient. Treatment for viral, bacterial, and fungal co-pathogens should be optimized.

A. GENERAL PRINCIPLES

a. Upper respiratory tract infection (URTI)

- i. Consider chest imaging to evaluate for lower respiratory tract infection.
- ii. If chest imaging normal and no symptoms (ie testing done for surveillance), no therapy is recommended at this time. Future clinical trials may enroll patients at the asymptomatic phase.
- iii. If chest imaging normal and mild upper respiratory symptoms (rhinorrhea, sore throat, etc), patients should be considered for clinical trials if available. Specific agents can be considered if symptoms progress. See [IV.B](#). Infectious diseases should be consulted.

b. Lower respiratory tract infection (LRTI)

- i. Given challenges around obtaining imaging and bronchoalveolar lavage fluid (BALF), we propose the following definitions of LRTI:
 1. Proven LRTI: Detection of SARS-CoV-2 by PCR in BALF with consistent radiographic changes
 2. Possible LRTI: Consistent radiographic changes OR presence of LRTI symptoms (cough, shortness of breath, hypoxemia) with a positive upper tract SARS-CoV-2 PCR test.
- ii. LRTI may be complicated by severe lung inflammation and the development of acute respiratory distress syndrome (ARDS).
- iii. LRTI from SARS-CoV-2 may be complicated by subsequent bacterial or fungal co-infection. Viral co-infection should also be considered and treated if agents available.
- iv. Therapy should be considered in patients with LRTI; agents may be added as combination therapy as severity increases. See [IV.B](#).
- v. Infectious diseases should be consulted.

B. TREATMENT CONSIDERATIONS

All recommendations are for both adult and pediatric patients unless otherwise indicated. Given lack of conclusive evidence of efficacy, treatment should be considered after careful consideration of drug interactions, drug toxicities and overall level of immunosuppression.

Table 1: Treatment considerations	
Disease stage	Treatment recommendations
Asymptomatic positive (if surveillance testing done)	Clinical trial if available
URTI only	1. Clinical trial if available 2. See section IV.C for additional considerations
LRTI without oxygen requirement	1. Clinical trial if available 2. See section IV.C for additional considerations 3. See discussion about antibiotics in section IV.D
LRTI with oxygen requirement or mechanical ventilation	1. Clinical trial if available 2. See section IV.C for additional considerations 3. See discussion about antibiotics, steroids, and IVIG in section IV.D

C. RATIONALE FOR USE OF SELECT AGENTS

Lack of conclusive data on clinical efficacy precludes specific recommendations, and patients should be enrolled in clinical trials whenever possible. Remdesivir, an investigational agent originally developed for Ebola virus, is being evaluated in several clinical trials and many centers may participate in these trials. If a clinical trial is not available or a patient is ineligible, first line therapies to consider include lopinavir/ritonavir, chloroquine (or hydroxychloroquine), or a combination of these, after careful consideration of toxicities and drug-drug interactions. **Toxicity may be enhanced with combination therapy.** Addition of ribavirin or other agents such as interferons should only be considered on a case-by-case basis in patients with severe disease. Drug availability is another important consideration. The following agents are not listed in any particular order of preference.

Remdesivir

- i. Mechanism of action: Nucleotide prodrug, inhibits RNA-dependent RNA polymerase and permanently terminates viral RNA transcription.
- ii. Efficacy demonstrated in in vitro and mouse model of MERS-CoV, SARS-CoV^{10, 11} and in in vitro models of SARS-CoV-2¹²
- iii. Clinical trials underway (NCT04257656, NCT04252664; NCT04280705, NCT04292899, NCT04292730, NCT04302766)
- iv. Compassionate use information: <https://rdvcu.gilead.com/>
 1. Key Inclusion criteria: Hospitalization, confirmed SARS-CoV-2 by PCR, invasive mechanical ventilation
 2. Key Exclusion criteria: Evidence of multi-organ failure, pressor requirement to maintain blood pressure, ALT levels > 5 X ULN, creatinine clearance <30 mL/min or dialysis or continuous veno-venous hemofiltration, use of other experimental antiviral agents for COVID-19.
- v. Adverse events: Transient elevations of transaminases, hypotension during infusion, reversible kidney injury (preclinical studies only)
- vi. Drug-drug interactions: No anticipated drug-drug interactions

Chloroquine/hydroxychloroquine

- i. Mechanism of action: Heme polymerase inhibitor; increases endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV
- ii. Efficacy: Inhibits SARS-CoV-2 in vitro¹², hydroxychloroquine more potent¹³; antiviral effect in newborn mice with MERS-CoV¹⁴; no antiviral effect seen in mice with SARS-CoV¹⁵. Reported success in 100 subjects in China with COVID-19: inhibited the exacerbation of pneumonia, improved lung imaging findings, promoted virus negative conversion, and shortened the disease course¹⁶. Hydroxychloroquine may have better efficacy¹³.
- iii. Clinical trials underway (NCT04261517, NCT04307693)
- iv. Adverse events: Nausea and diarrhea, hypoglycemia, agranulocytosis, LFT abnormalities
- v. Drug-drug interactions: Caution with concomitant Qtc prolonging drugs

Lopinavir/ritonavir

- i. Mechanism of action: Protease inhibitors; lopinavir inhibits activity of the protease enzyme; ritonavir is a pharmacologic booster, resulting in increased concentrations of lopinavir via decreased hepatic and GI metabolism of lopinavir
- ii. Efficacy: In SARS-CoV, early LPV/r (with ribavirin) associated with increased survival and lower need for pulse steroids¹⁷, ARDS or death as outcome reduced, progressive decrease in viral load, early rise in lymphocyte count, reduction in cumulative dose of pulsed steroids, and fewer nosocomial infections¹⁸.
- iii. Clinical trials underway (NCT04255017, NCT04276688, NCT04307693)
- iv. Adverse events: Moderate diarrhea and nausea, LFT abnormalities, potential for pancreatitis, hyperglycemia
- v. Drug-drug interactions: including but not limited to amiodarone, cyclosporine, tacrolimus, phenytoin, rifampin, voriconazole, simvastatin and others). Caution with concomitant Qtc prolonging drugs. Consultation with clinical pharmacy team is warranted to manage associated drug interactions.

Ribavirin

- i. Mechanism of action: Nucleoside inhibitor, guanine derivative and inhibits RNA polymerase and viral protein synthesis.
- ii. Efficacy: Used as combination therapy with interferon for MERS-CoV¹⁹, no difference in multivariable analyses compared to no therapy. Not recommended as monotherapy. Dose listed is that recommended for RSV; higher doses have been used in SARS. Currently no data on optimal dosing is available and caution is advised given toxicity profile.
- iii. Clinical trials underway as combination with IFN-beta and lopinavir/ritonavir (NCT04276688)
- iv. Adverse events: Hemolytic anemia, headache, diarrhea, abdominal pain, neutropenia

D. ADJUNCTIVE THERAPIES

Corticosteroids

Data on the use of corticosteroids for COVID-19 is mixed and difficult to interpret give variability in time of administration and dosing. In SARS-CoV, any steroid therapy was associated with increased need for ICU admission or mortality²⁰, although lower mortality and shorter hospitalization was seen among critical cases²¹ and pulse steroids resulted in lower oxygen requirements and better radiographic outcomes compared to non-pulsed steroids²². In MERS-CoV, however, steroid therapy was evaluated both by dose and duration and no effect was seen on mortality; however, increased time to RNA clearance was observed²³. One study of SARS-CoV-2 suggests, delayed use of steroids may increase risk of death in the ICU²⁴. In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death²⁵; short courses of low-moderate dose steroids has also been recommended in critically ill patients²⁶. Given the uncertainty of optimal timing of steroid therapy, and potential for steroid therapy to worsen disease severity and lead to secondary infections in the immunocompromised population, routine use of steroids is not recommended at this time in patients with mild disease. Use of steroids in patients with severe disease (requiring oxygen support or mechanical ventilation) should be considered as part of the supportive care regimen for patients with ARDS on a case-by-case basis with an ICU specialist.

IVIG

Currently available IVIG products are unlikely to contain specific antibodies to SARS-CoV-2, and thus are unlikely to improve clinical disease via a direct neutralizing antibody effect. IVIG has been suggested to have anti-inflammatory or immunomodulatory effects; however, given the lack of conclusive clinical data for treatment of coronaviruses and national shortage of IVIG products, **routine use of IVIG is not recommended** at this time.

Antibiotics

Hospitalized adults in China were frequently treated with antibiotics²⁴, although the true incidence of bacterial super- or co-infection has not been fully characterized. We do not recommend routine antibiotic use in patients for patients with SAR-CoV-2 limited to the upper respiratory tract, unless indicated for other reasons according to local protocols (i.e. management of febrile neutropenia). Given recommendations against routine BAL and limited ability to make a microbiologic diagnosis, empiric antibiotic use can be considered for LRTI on an individual basis. Important considerations include level of immunosuppression including neutropenia and baseline steroid use/other immunosuppressive agents for GVHD, radiographic appearance, and illness severity. These factors should determine the urgency to evaluate co-infections (early CT scan and BAL, diagnostic testing for other pathogens, and empiric use of antibacterial/antifungal agent), which are not uncommon in this patient population.

E. OTHER AGENTS UNDER CONSIDERATION

Interferons

Several interferons and formulations of interferons have been used for treatment of COVID-19, mostly as combination therapy^{19, 27}. A recent randomized controlled trial of IFN-beta-1a for treatment of ARDS did not show improvement in death or ventilator free days²⁸. There is insufficient evidence to support routine use of interferon therapy; however, may be considered in individual circumstances.

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor that inhibits IL-6 mediated pro-inflammatory response. In an open-label study in 21 patients in China with documented COVID-19 and severe oxygenation impairment, including high flow oxygen and intubation, tocilizumab reduced oxygen requirement, normalized the CRP, and increased the lymphocyte count to normal; 19 of the 20 patients were discharged²⁹. Routine use is not recommended, future clinical trials are needed to assess efficacy and toxicity profile. Adverse reactions: LFT abnormalities, local injection site reactions, increased risk of serious infections seen with long term use. Clinical trials are ongoing (NCT04310228, ChiCTR2000029765).

Angiotensin-receptor blockers and Angiotensin converting enzyme blockers

SARS-CoV-2 uses ACE2 receptor for cell entry in the lungs and thus the course of the infection could be impacted by concurrent use of these antihypertensive agents. Furthermore, ACE2 itself is protective against lung injury, thus reduced levels may exacerbate pulmonary complications³⁰. Experts appear to vary whether they believe that these drugs would exacerbate or ameliorate COVID-19 disease. No clinical data are available yet to suggest that these drugs should be started or stopped in patients with SARS-CoV19 infection. The Council on Hypertension of the European Society of Cardiology strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive therapy. There is not enough data to support use of this class of drugs for treatment. Clinical trials, including of recombinant ACE2, are ongoing (NCT04287686).

Table 2: Dosing recommendations			
Agent	Adult dose	Pediatric dose	Main toxicities
Lopinavir/ritonavir	400 mg/100 mg PO q12h for 10 days	<p><i>All doses are based on the lopinavir component:</i></p> <p><i>Suspension</i> <15 kg: 12 mg/kg/dose PO q12h for 10 days 15-40 kg: 10 mg/kg/dose PO q12h for 10 days >40kg: 400 mg PO q12h for 10 days</p> <p><i>Able to tolerate tablets</i> ≥15-25 kg: 200 mg PO q12h for 10 days 25-35 kg: 300 mg PO q12h for 10 days >35 kg: 400 mg PO q12h for 10 days</p>	Potential drug interactions (CNI, mTOR inhibitors, azoles); moderate diarrhea and nausea; LFT abnormalities
Hydroxychloroquine	400mg PO BID on day 1, followed by 200mg PO BID on days 2-5	Doses will approximate 6.5 mg/kg/dose for load, 3.25 mg/kg/dose for maintenance 10-23kg: 100 mg PO 2x/ day for 1 day, followed by 50 mg PO 2x/ day for 4 days >23kg-40kg: 200mg PO 2x/ day for 1 day, followed by 100 mg PO 2x/ day for 4 days >40kg-54kg: 300mg PO 2x/ day for 1 day, followed by 150 mg PO 2x/ day for 4 days >54kg: 400mg PO 2x/ day for 1 day, followed by 200 mg PO 2x/ day for 4 days	Nausea and diarrhea, agranulocytosis, LFT abnormalities, QTc prolongation, bone marrow suppression, retinal toxicity (with prolonged duration)
Chloroquine	500 mg PO q12h for 10 days	Doses for chloroquine phosphate approximate 8.3mg/kg/dose >15kg: 125mg PO q12h for 10 days 15-45kg: 250mg PO q12h for 10 days >45kg: 500mg PO q12h for 10 days	
Ribavirin	1200 mg PO x1 then 600 mg q8h for 10 days (see text above for dose discussion)	15mg/kg PO x 1, then 7.5mg/kg PO q8h for 10 days (see text above for dose discussion)	Hemolytic anemia, headache, diarrhea, abdominal pain, neutropenia

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