

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

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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, exposure to a known case of COVID-19, or travel history to a high-risk area as defined by the CDC², the following evaluations should be performed. If testing not available, risk should be ascertained based on exposure history per current CDC definitions.

- 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 Centers for Disease Control (CDC) recommendations for swab collection².
 - 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 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 IV).

III. TREATMENT CONSIDERATIONS FOR HCT AND CELLULAR THERAPY PATIENTS:

There are no approved therapies for the treatment of COVID-19. Several drugs have been studied in prior coronavirus outbreaks (SARS-CoV and MERS-CoV) and though some benefit has been demonstrated, the data are inconclusive. Currently, there are several drugs being evaluated in clinical trials in several nations including lopinavir/ritonavir, ribavirin, hydroxychloroquine, darunavir/cobistat and interferons alpha and beta. In addition, several investigational agents are being evaluated, including remdesivir, which is being evaluated in an NIH-sponsored placebo controlled clinical trial in the United States⁵. This and other agents may be available through compassionate use programs. At this point no recommendations can be made on specific therapies due to limited data and unknown risk vs benefit; additional recommendations will be forthcoming. Even less data is available for pediatric patients. Treatment for viral, bacterial, and fungal co-pathogens should be optimized.

A. General principles

a. SARS-CoV-2 detected in upper tract sample

- i. Consider chest imaging as above
- ii. If chest imaging normal and no symptoms (ie testing done for surveillance), no therapy is recommended.
- iii. If chest imaging normal and mild upper respiratory symptoms (rhinorrhea, sore throat, etc), no therapy is recommended but can be considered if symptoms progress. Infectious diseases should be consulted.
- iv. If chest imaging abnormal and/or lower tract symptoms, see section II.D for additional diagnostic guidance; consider therapy. Infectious diseases should be consulted.

b. SARS-CoV-2 detected in BAL

- i. Consider therapy. As above, no specific recommendations can be given at this time. Priority should be given for participation in clinical trials. Infectious diseases should be consulted.

IV. CONSIDERATIONS FOR EVALUATION PRIOR TO HCT OR CELLULAR THERAPY

(Adapted from EBMT guidelines published 3/2/2020)⁶

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 to areas designated as high-risk areas by the WHO and the CDC².
- e. In HCT and cellular therapy candidates who have traveled to a high-risk area or had close contact with a person travelling from a high-risk area for COVID-19, 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. If the candidate has at least two consecutive negative PCR tests each approximately one week apart (deferral for 14 days minimum), proceeding with procedures can be considered.
- f. 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.
- a. 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 therapies⁷. 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 severity⁸. Current American Association of Blood Banks guidelines do not recommend screening for SARS-CoV-2 in blood products⁹ and current Food and Drug Administration guidelines recommend considering the donor's infection and exposure history in the 28 days prior to donation¹⁰. 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. In donors with travel to high-risk areas for COVID-19 or with close contact with a person travelling from such an area, 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.
- d. 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.”

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

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