

CORONAVIRUS DISEASE COVID-19: EBMT RECOMMENDATIONS **UPDATE MARCH 16, 2020**

A novel coronavirus named SARS-CoV-2 of a zoonotic origin emerged in the beginning of this year and the infection called Coronavirus Diseases 2019 (COVID-19) started spreading worldwide. The WHO is now calling this a pandemic with increasing number of cases in many countries in Europe and elsewhere.

Many European countries have imposed major restrictions on meetings, travel, and everyday life. This is likely to impact greatly on the transplant activity in Europe as in many other parts of the world. The severity of the disease varies a lot with many individuals having very few symptoms while elderly having comorbid conditions being at the greatest risk for mortality especially in Acute Respiratory Distress Syndrome (ARDS). As of today, no clear information of the impact on transplant patients exists and there is yet no report on PubMed regarding a stem cell transplant patient developing COVID-19 and the outcome of the disease.

Incubation period: Time from exposure to symptom development is between 2-14 days.

Prophylaxis and treatment: Avoiding exposure by adhering to recommended hygiene procedures, isolation of SARS-CoV-2-infected persons and social distancing are the only prevention strategies (see: Box 1. The WHO recommendations).

Currently there is no approved treatment options in Europe and there is no available vaccine. In some countries, remdesivir might be available for compassionate use for the most severe cases. Remdesivir has demonstrated *in vitro* and *in vivo* activity in animal models against the viral pathogens MERS and SARS, which are also coronaviruses and are structurally similar to SARS-CoV-2. The limited preclinical data on remdesivir in MERS and SARS indicate that remdesivir may have potential activity against COVID-19. Anti-retroviral therapy (lopinavir/ritonavir) and hydroxychloroquine have also been used in some cases.

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. There are ongoing clinical trials in different countries. Tocilizumab has also been used in China for therapy of severe cases suspected having cytokine associated pathology.

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.

EBMT guidelines: Due to fast spreading of SARS-CoV-2 a panel of experts of EBMT recommends the following guidelines for recipients and donors of hematopoietic cells before the beginning of any of the transplant procedures (mobilization, apheresis, marrow harvest, and conditioning). These guidelines will be updated when new information is obtained about COVID-19 epidemiology and clinical outcome.

Prevention policies and procedures: This document will not cover specific infection prevention policies and procedures; national, local and institutional guidelines should be followed. In the setting of known high community prevalence of SARS-CoV-2, clinic visits that are not critical should be either deferred or substituted with telemedicine visits if deemed appropriate and feasible. It is logical to ask stem cell transplanted patients to restrict their risk of exposure to infected individuals as much as possible and to be very careful with hygienic routines including hand washing and use of alcohol containing hand sanitizers.

Scheduling transplant procedures: Due to the rapidly changing situation, access to a stem cell donor might be restricted either due to the donor becoming infected, logistical reasons at the harvest centers in the middle of a strained health care system, or travel restrictions across international borders. It is therefore strongly recommended to have secured stem cell product access by freezing the product before start of conditioning and in situations when this is not possible, to have an alternative donor as a back-up. For low risk patients, it is recommended to postpone the start of the transplant procedure if deemed to be safe to do so. This includes both allogeneic and autologous transplant procedures.

Diagnostic procedures: Should be according to national guidelines. Patients, who reside in an area with high risk of transmission of SARS-CoV-2 or who have been in close contact to a person to such areas should be tested for the virus. It is important to note that a test for SARS-CoV-2 can be false negative and needs to be repeated if there is a strong suspicion of COVID-19 such as case of pneumonia or severe illness. It is also important to test for other respiratory viral pathogens including influenza and RSV preferably by multiplex PCR.

All patients positive for SARS-CoV-2 in an upper respiratory tract sample should undergo chest imaging and evaluation of oxygenation impairment.

Routine bronchoalveolar lavage (BAL) is not recommended if patient tested positive with SARS-CoV-2 given risk of transmission amongst health care workers, unless a co-infection is suspected. If chest imaging 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.

Please, report all cases in the prospective EBMT survey. The form can be obtained from idwp.ebmt@lumc.nl

Recommendation recipients:

1. Stem cell transplanted patients should restrict their risk of exposure to infected individuals as much as possible and to be very careful with hygienic routines including hand washing and use of alcohol containing hand sanitizers.
2. Stem cell transplant patients should refrain from non-necessary travel according to national guidelines.
3. In case of diagnosis of COVID-19: In patients with no or only upper respiratory symptoms, no therapy is recommended. In patients with lower respiratory tract symptoms, the possibilities of installing therapy should be investigated with participation in a clinical trial recommended if possible.
4. According to ECDC recommendations, patients ought to be deferred for at least three months. However, this is not always possible due to the risk from the underlying disease. Therefore, in patients with high risk disease, HCT should be deferred until the patient is asymptomatic and has three repeated virus PCR negativity at least one week apart (deferral of 14 days minimum). In patients with low risk disease a three month HCT deferral is recommended.
5. In case of residing in a high-risk area, patients planned to be admitted for a transplant should try to minimize the risk by home isolation 14 days before the start of the transplant conditioning. All patients should be tested before start of the conditioning regardless of whether upper respiratory symptoms are present.
6. In case of close contact with a person diagnosed with COVID-19 any transplant procedures (PBSC mobilization, BM harvest, conditioning) shall not be performed within at least 14 preferably 21, days from the last contact. Patient should be closely monitored for the presence of COVID-19, with confirmed PCR negativity.
7. In case of having been to a high risk area or having been in close contact with person travelling from a high risk area for COVID-19 as defined by national authorities, ECDC, or WHO, any transplant procedures (PBSC mobilization, BM harvest, and conditioning) should not be performed within at least 14 preferably 21 days from the last contact.

Recommendations 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 therapies. WMDA has produced recommendations and the EBMT endorses these guidelines.

1. In case of diagnosis of COVID-19, donor must be excluded from donation. At this time it is not possible to give recommendations when such an individual can be cleared for donation but at least three months deferral can be considered unless the need for donation is urgent when individual consideration should be made.
2. In case of close contact with a person diagnosed with SARS-CoV-2, the donor shall be excluded from donation for at least 28 days. Donor should be closely monitored for the presence of COVID-19.
3. If the patient's need for transplant is urgent, the donor is completely well and there are no suitable alternative donors, earlier collection may be considered subject to careful risk assessment if local quarantine requirements permit
4. In case of travel to high risk areas for COVID-19 (as defined by health authorities*) or being a close contact with person travelling from such an area, donor shall be excluded from donation for at least 28 days.

5. Donors within 28 days before donation should practice good hygiene (see: Box 1. The WHO recommendations) and avoid crowded places and large group gatherings.

Box 1. The WHO recommendations on how to protect yourself and the others from COVID-19

1. Wash your hands frequently with an alcohol-based hand rub or with soap and water.
2. Maintain social distancing of at least 1 meter between yourself and anyone who is coughing or sneezing.
3. Avoid touching eyes, nose and mouth.
4. Practice respiratory hygiene (covering your mouth and nose with your bent elbow or tissue when you cough or sneeze and then dispose of the used tissue immediately).
5. If you have fever, cough and difficulty breathing, seek medical care early, but call in advance and follow the directions of your local health authority.
6. Stay informed and follow advice given by your healthcare provider, your national and local public health authority since they can provide you with reliable information on whether COVID-19 is spreading in your area.
7. Additionally, in case of persons who are in or have recently visited (past 14 days) areas where COVID-19 is spreading, stay at home if you begin to feel unwell, even with mild symptoms, until you recover, but if you develop fever, cough and difficulty breathing, seek medical advice promptly by calling your health provider to so you can be quickly directed to the right health facility.

Updated information see: (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_4)

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