

CORONAVIRUS DISEASE COVID-19: EBMT RECOMMENDATIONS **UPDATE MARCH 30, 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 classified COVID-19 a pandemic on March 19 with rapidly increasing number of cases in many countries in Europe and elsewhere. The pressure on the health care system is very high in several countries and increasing numbers of infected health care staff are being reported. 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.

COVID-19: Time from exposure to symptom development is between 2-14 days (median 5 days). Symptoms vary from no or very mild symptoms of an upper respiratory infection to very severe resulting in the need for intensive care and death from Acute Respiratory Distress Syndrome (ARDS). The risks both for infections and for severe disease seem to be low in children. Increasing age and the presence of comorbidities, such as hypertension, cardiovascular disease, diabetes, and pulmonary disease, are reported risk factors for severe disease and mortality.

EBMT guidelines: Due to fast spreading of SARS-CoV-2 a panel of experts of EBMT recommends the following guidelines for transplant units, recipients, and donors of hematopoietic cells. These guidelines will be updated when new information is obtained about COVID-19 epidemiology and clinical outcome.

Prevention policies and procedures: National, local and institutional guidelines should be followed. 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).

Transplant centers: Visitors should be restricted as much as possible. No visitor with respiratory symptoms should be allowed. Staff with respiratory symptoms should stay at home. Testing of staff should be done according to national and local guidelines. In the setting of known high community prevalence of SARS-CoV-2, outpatient visits that are not critical should be either deferred or substituted with telemedicine visits if deemed appropriate and feasible. Training of staff in proper procedures, including caring for those with suspected or confirmed infection, ensuring adequate access to personal protection equipment and planning for possible staff shortage are critical.

Scheduling transplant procedures. Non-urgent transplants should be deferred as much as possible, especially for non-malignant disorders. 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. Peripheral blood should be preferentially used unless there is a strong indication for bone marrow.

Recommendation transplant candidates:

1. Patients planned to be admitted for a transplant or to undergo CAR-T cell therapy should try to minimize the risk by home isolation 14 days before the start of the transplant conditioning. Non-necessary clinic visits should be avoided.
2. All patients should be tested for SARS-CoV-2 and the test results should be negative before start of the conditioning regardless of whether upper respiratory symptoms are present.
3. If a transplant candidate/patient with planned CAR-T cell therapy is diagnosed with COVID-19, patients ought to be deferred for at least three months according to ECDC recommendations. However, this is not always possible due to the risk for progression of the underlying disease. Therefore, in patients with high risk disease, HCT should be deferred until the patient is asymptomatic and has two repeated virus PCR negativity at least 24 hours apart. Deferral of 14 days is minimum but should preferably be 21 days and a new PCR is recommended before start of conditioning. In patients with low risk disease a three-month HCT deferral is recommended.
4. 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, and preferably 21, days from the last contact. Patient should be closely monitored for the presence of COVID-19, with confirmed PCR negativity before any transplant procedure is undertaken.

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 three-month deferral can be considered unless the need for donation is urgent, and case-specific considerations 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, a test is negative for SARS-CoV-2 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.

Recommendations stem cell transplant and CAR-T cell recipients:

1. Stem cell transplanted patients and patients having undergone CAR-T cell therapy should limit their risk of exposure to infected individuals as much as possible and strictly adhere to prevention practices such as hand hygiene and social distancing.

2. Stem cell transplant patients should refrain from travel according to national guidelines and, if travel is absolutely necessary, travel by private car instead of train, bus, or plane is recommended if feasible.
3. Diagnostic procedures should follow national or local guidelines. Patients, who reside in an area with high risk of transmission of SARS-CoV-2 or who have been in close contact with a person from such areas should be tested for the virus. It is important to note that a test for SARS-CoV-2 in nasopharyngeal swab can be falsely negative and needs to be repeated if there is a strong clinical suspicion of COVID-19. The performance of testing is higher in lower than in upper respiratory tract. It is also important to test for other respiratory viral pathogens including influenza and RSV preferably by multiplex PCR.
4. All patients positive for SARS-CoV-2 in an upper respiratory tract sample should undergo chest imaging, preferably by CT, and evaluation of oxygenation impairment.
5. Routine bronchoalveolar lavage (BAL) is not recommended if a patient tested positive for SARS-CoV-2 given risk of transmission amongst health care workers, unless a co-infection is suspected. Co-pathogens should be evaluated and treated.

Treatment:

Currently there is no approved treatment options in Europe and there is no available vaccine. 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. Chloroquine and hydroxychloroquine have also been used with data suggesting reduction of viral load and have been used for therapy with some encouraging results although controlled trials are lacking. There is also some data for combination of chloroquine with azithromycin. 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. Lopinavir/ritonavir has also been used but a recently published trial failed its primary endpoint. Several clinical trials are ongoing.

Since an important part of the pathology seems to be cytokine release, different therapies addressing this syndrome have been tested. Tocilizumab, which is approved for cytokine release syndrome after CAR-T cell therapy, have been used and is approved in China. Data on the use of corticosteroids are contradictory. Corticosteroid therapy was associated with lower mortality in immunocompetent patients with ARDS.

Some data suggest that use of angiotensin conversion enzyme inhibitors and angiotensin II receptor blocker might be implicated in development of renal failure in COVID-19 patients. There is not enough data at present to recommend discontinuation of these drugs. Similarly, it has been suggested that NSAIDs might have negative effects and therefore acetaminophen/paracetamol are preferred as anti-pyretics.

At this point no clear recommendations can be made on specific therapies due to limited data and unknown risk vs benefit. Even less data is available for pediatric patients. Please, see the slides from the EBMT webinar presented on March 20 available on the EBMT website (www.ebmt.org) for more details and the most recent publications on treatment option on: <https://www.nejm.org/coronavirus> and/or <https://www.thelancet.com/coronavirus>

In case of diagnosis of COVID-19 infection:

1. It is unclear if patients with no or only mild upper respiratory symptoms benefit from therapy.
2. In patients with progressing symptoms or lower respiratory tract symptoms, the possibilities of starting therapy should be investigated, with participation in a clinical trial recommended if possible. The best data currently exist for chloroquine or hydroxychloroquine, with increasing experience of use from several centers. Combination therapy has also been used. Remdesivir has been used as compassionate therapy in more severe cases.
3. Antiinflammatory therapy can be considered in more severe cases.
4. Treatment of viral, bacterial, and fungal co-pathogens should be optimized.
5. Immunosuppressive prophylaxis / treatment should be continued.

Please, report all diagnosed cases in the prospective EBMT survey both regarding transplant and CAR-T cell treated patients. The form can be obtained from idwp.ebmt@lumc.nl. As of March 27, 38 patients have been reported and we are collecting follow-up data, which we hope will be useful for preparing future versions of these guidelines. We realize that the time at transplant centers is very limited but it would be of value to learn more ASAP and therefore if you have a chance, please, register your patients and fill in the follow-up forms.

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/20200328-sitrep-68-covid-19.pdf?sfvrsn=384bc74c_2)*

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