

CORONAVIRUS DISEASE COVID-19: EBMT RECOMMENDATIONS

VERSION 9 – June 15, 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. **Several countries have now lifted restrictions to varying degrees. Several small outbreaks have been documented after lifting of restrictions.** It is crucial that vigilance is maintained in the management of stem cell transplant recipients.

The necessity to obtain valuable data about SARS-CoV-20 has put high pressure on both authors and editors. Thus, interpretation of rapidly published data has to be careful and put in context.

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: Since the COVID-19 situation varies substantially between and within countries, we recognize that centers are mandated to follow guidelines, policies, and procedures decided by national authorities as well as local and institutional policies. Avoiding exposure by adhering to recommended hygiene procedures, isolation of SARS-CoV-2 infected individuals, and social distancing especially for risk groups are currently the main prevention strategies utilized in most European countries. Limiting exposure of healthcare personnel and mitigating the psychological consequences of altered and stressful working conditions is another high priority to ensure that appropriate capacities remain available to treat patients in the middle- to long-term. **Continued vigilance is crucial after restrictions in the society have been lifted and appropriate testing is strongly recommended.**

Staff with any symptoms of infection should stay at home. Testing for SARS-CoV-2 is strongly recommended since symptoms can be uncharacteristic and very mild. Return to work by staff, who have recovered from COVID-19 should follow national guidelines, usually requiring the resolution of symptoms and two negative PCR results.

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. Personal protective equipment especially masks are important to limit the spread and to reduce the risk for health care workers to become infected. Surgical masks protect mainly for transmission of the virus from an infected individual while certain masks of the FFP2/3 class (those with an exhalation valve) protect the wearer of the mask but may not prevent from transmitting the virus. An FFP2/3 mask without exhalation valve also prevents from transmitting and is an alternative. Thus, correct selection of the mask and correct use are crucial.

Outpatient visits and visitors: Outpatient visits should be ~~as much as possible either deferred or~~ substituted with telemedicine visits if deemed appropriate and feasible. **For necessary out-patient visits, it is important that appropriate measures to reduce the risk for nosocomial transmission are applied.** Staff should preferably be dedicated to a COVID-19 free transplant unit and not used interchangeably to care for COVID-19 positive patients. It is critical that proper protective equipment is used as recommended by national and international competent authorities.

Since the risk of a resurgence of COVID-19 after lifting of restrictions remains unknown, it is recommended to maintain visitor restrictions in ~~No visitors should be allowed in transplant units.~~ There might be exceptions for parents to transplanted children; testing for SAR-CoV-2 should then be considered before entering the ward. Repeated testing might then be necessary. This will bring its own set of challenges when attempting to have end of life conversations with families who will not be present in person.

Patients after HCT

Considerations in HCT and CAR T-cell recipients still being regarded as immunosuppressed or having significant organ dysfunction: They 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. Stem cell transplant patients should refrain from travel and if travel is deemed necessary, travel by private car instead of any public transportation system including train, bus, or plane is recommended if feasible.

Physical and social isolation, although a usual practice for many transplant patients, will now extend further and for a longer period of time and local services and practices need to be explored by the nursing staff to ensure that patients have adequate provision to be cared for at home.

All patients, including those without symptoms, should be triaged and tested before entering the transplant ward. Adequate space for symptomatic patients while awaiting the results of COVID-19 testing should be allocated preferably separate from the transplant unit.

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. Unnecessary clinic visits should be avoided.

Transplant candidates

It is recognized that patients might suffer harm if transplant and other treatment procedures are delayed due to COVID-19. It is not possible to give clear guidelines regarding which procedures should be delayed since the epidemiological situation of SARS-CoV-2 circulation in the communities is highly variable between transplant centers. Before starting the

transplant procedure, availability of adequately trained staff, ICU beds, ventilators, as well as availability of the stem cell product should be ensured. **In countries that still have ongoing coronavirus transmission in the community,** non-urgent transplants should be deferred as much as possible, especially for non-malignant disorders. **For countries where no significant coronavirus transmission exists, stepwise return to normal practice can be considered but vigilance is needed if transmission recurs.** For those that will have delays in treatment, signposting to appropriate local advice and support groups is of paramount importance.

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.

A difficult question based on lack of data is deferral of transplant candidates if they become infected with COVID-19. The decision has to be made based on individual considerations taking into account the risk of the patient associated with on one hand the delay of the procedure and on the other proceeding with conditioning. In general, however, if a transplant candidate is diagnosed with COVID-19 a deferral of at least three months is advisable, in accordance with ECDC recommendations. However, this is not always possible due to the risk for progression of the underlying disease. This might be particularly pertinent for patients waiting for CAR T-cell therapy since this is frequently performed on patients refractory for other therapies and therefore being at a very high risk for progress of the underlying disease. Therefore, in patients with high risk disease, stem cell transplantation should be deferred until the patient is asymptomatic and has two negative virus PCR swabs taken at least 24 hours apart. **It might also be advisable to allow enough time for the lung function and general performance to have returned to pre-COVID-19 values or at least have improved compared to the situation during the COVID-19 disease.** Deferral of 14 days is a minimum but should preferably be 21 days and a new PCR is recommended before the start of conditioning. In patients with low risk disease a three-month HCT deferral is recommended. Individual considerations have to be made for CAR T-cell patients.

In case of close contact with a person diagnosed with COVID-19 any transplant procedures (PBSC mobilization, BM harvest, and 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.

Donor considerations

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.

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 therapies¹. WMDA has produced recommendations and the EBMT endorses these guidelines.

In case of diagnosis of COVID-19, donor must be excluded from donation. Collection should be deferred for at least 28 days after recovery. If the patient's need for transplant is urgent, the donor is completely well and there are no suitable alternative donors, an earlier collection may be considered if local public health requirements permit*, subject to careful risk assessment. Risk assessment should be based on: the date of full recovery, the duration and severity of COVID-19, and the results of post-recovery testing.

*Note that there is evidence that SARS-CoV-2 RNA can remain detectable by PCR in nasopharyngeal samples for an extended period after full recovery. Nasopharyngeal shedding does not equate to viremia, and other coronaviruses (including SARS-CoV-1 and MERS-CoV) have not displayed transmissibility via blood or HPC. Nonetheless, a donor with detectable nasopharyngeal SARS-CoV-2 RNA could be considered a potential infective risk to staff and other donors at a collection centre.”

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. 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.

Donors within 28 days of donation should practice good hygiene and be as socially isolated as feasible during this period. Unnecessary travel should be avoided. Donors should have been asymptomatic for at least 14 (preferably 21) days before donation. It is recommended that donors are tested for COVID-19 prior to starting the mobilization procedure if non-frozen cells are planned to be used. Stem cell products can also be frozen at the harvest site if the transport is expected to be prolonged.

DIAGNOSIS AND MANAGEMENT OF COVID-19

Diagnosis of COVID-19

Diagnostic procedures for COVID-19 should follow national or local guidelines. 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 better in samples from the lower than from the upper respiratory tract (sputum or bronchoalveolar lavage). It is also important to test for other respiratory viral pathogens including influenza and RSV preferably by multiplex PCR.

SARS-CoV-2 infected patients,

Patients, who are positive for SARS-CoV-2 should not be treated in rooms with laminar air flow or other rooms (HEPA) with positive pressure unless the ventilation can be turned off. 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. 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

Treatment of COVID-19 positive transplant recipients and CART-cell patients: 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. 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-19²⁻⁴. Remdesivir has been approved in the USA and Japan

for treatment of COVID-19 and the EMA has granted compassionate use. One randomized clinical trial from China did not show improvement, while in a randomized trial from the US in 1063 patients remdesivir shortened the time to recovery in adults with Covid-19 pneumonia, with non statistically significant impact on mortality (7.1% vs. 11.9%)⁵. Lopinavir/ritonavir has also been used but a published trial failed its primary endpoint^{3,6}. A combination of lopinavir/ritonavir with ribavirin and interferon-beta was reported to improve viral clearance and alleviation of symptoms compared to lopinavir/ritonavir given alone⁷. Chloroquine and hydroxychloroquine have also been used with data suggesting reduction of viral load and have been used for therapy with varying results and toxicity^{2,8-11}. Several competent authorities have warned about the risk for severe side effects especially cardiac side effects (QT prolongation, particularly if other QT prolonging drugs are co-administered) and some competent authorities warn against use especially in outpatients. Hydroxychloroquine given as postexposure prophylaxis in a randomized trial did not reduce the risk for Covid-19. Nonetheless, due to several methodology questions the results of this trial are more provocative than definitive, suggesting that the potential prevention benefits of hydroxychloroquine remain to be determined. EMA recommends that these drugs should be given in the context of a clinical trial. More studies are ongoing. Interferon- α is also being studied.

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^{12,13}. ~~Data on the use of corticosteroids are contradictory.~~ Short-term corticosteroid therapy was associated with lower mortality in immunocompetent patients with COVID-19 associated ARDS. Several other anti-inflammatory treatments are being studied.

Some data suggest that use of angiotensin conversion enzyme inhibitors and angiotensin II receptor blocker might be implicated in development of organ failure in COVID-19 patients^{14,15} but lower mortality has also been reported with the use of these drugs¹⁶. Therefore, discontinuation of these drugs is not recommended. 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. Therapy should be given in close collaboration with specialists in infectious diseases. Despite FDA approval of remdesivir, it is still unclear how it optimally should be used. Later in the course of the infection anti-inflammatory therapy with corticosteroids and/or tocilizumab has been shown to be of value in non-transplant patients. Supportive care is crucial including non-invasive ventilation and anti-coagulants to prevent thromboembolic complications, which can be frequent and severe in patients with Covid-19. Treatment of viral, bacterial, and fungal co-pathogens should be optimized. It is currently recommended that immunosuppressive prophylaxis / treatment is continued since there is no data supporting reducing immunosuppression and it might instead cause harm.

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 June 11, 246 patients have been reported from 18 countries and** we are collecting follow-up data, which we hope will be useful for preparing future versions of these guidelines. Preliminary data is showing approximately 30% mortality in both allogeneic and autologous HCT recipients. **Please, register patients and, in particular, fill-in the follow-up forms to allow analysis of the data.**

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.

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REFERENCES

1. Chang L, Yan Y, Wang L. Coronavirus Disease 2019: Coronaviruses and Blood Safety. *Transfus Med Rev.* 2020.
2. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-271.
3. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun.* 2020;11(1):222.
4. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem.* 2020.
5. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
6. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med.* 2020.
7. Zhu W, Wang Y, Xiao K, et al. Establishing and Managing a Temporary Coronavirus Disease 2019 Specialty Hospital in Wuhan, China. *Anesthesiology.* 2020.
8. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.* 2020.
9. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov.* 2020;6:16.
10. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect.* 2020.
11. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open.* 2020;3(4):e208857.
12. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv.* 2020;4(7):1307-1310.
13. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents.* 2020:105954.

14. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med.* 2020;46(4):586-590.
15. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med.* 2020.
16. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res.* 2020.