



CORONAVIRUS DISEASE COVID-19: EBMT RECOMMENDATIONS

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Coronavirus Diseases 2019 (COVID-19) have spread worldwide during the last six months and now almost 27 million cases have been diagnosed worldwide. The pressure on the health care system was very high in several countries and many European countries imposed major restrictions on meetings, travel, and everyday life. These restrictions resulted in a decline in the number of cases in most countries and therefore from the beginning of the summer 2020, restrictions were lifted in most European countries. However, both a more general increase in the number of cases and localized outbreaks have occurred in several countries although the number of deaths has been lower than during the first months of the pandemic.

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 severe pneumonia 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, obesity, 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. This is now the 10th version of the guidelines and we plan to continue to update them when new information is obtained about COVID-19 epidemiology and clinical outcome impacting on stem cell transplant (HCT) recipients or patients treated with CAR T cells.

EBMT registry: The EBMT started early in the pandemic to collect data regarding the impact of COVID-19 on HCT recipients and on CAR T cell treated patients. This was done in

close collaboration with the Spanish group (GET). As of September 1, 2020 more, than 400 patients have been registered from 21 countries and data have been presented at the recent virtual EBMT congress. The 6-week mortality is approximately 19% in autologous and 24% in allogeneic HCT recipients. The data collection is ongoing, and we urge centers to continue to report their patients and send us follow-up information.

GENERAL CONSIDERATIONS

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. Face mask use is also mandatory in most countries although the exact regulations vary.

Healthcare personnel have worked very hard over several months and although the pressure has decreased, it is still important to mitigate the psychological consequences of altered and stressful working conditions to ensure that appropriate capacities remain available to treat patients long-term.

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 members 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 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 continue to be 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.

The risk for transmission currently varies a lot between different European countries. In countries or regions within countries where there is substantial COVID-19 activity, it is recommended to maintain visitor restrictions to 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 or CAR T cell therapy: HCT and CAR T-cell recipients still being regarded as immunosuppressed or having significant organ dysfunction 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. These patients should refrain from travel and if travel is deemed necessary, travel by private car instead of any public transportations 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 being admitted to a transplant ward. Adequate space for symptomatic patients while awaiting the results of COVID-19 testing should be allocated preferably separate from the transplant unit. Furthermore, appropriate protocols for their care should be in place.

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. Today most transplant centers have returned to more or less normal transplant activity. It is not possible to give clear guidelines regarding if procedures should still 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.

All patients should be tested for SARS-CoV-2 by PCR and the test results should be negative before start of the conditioning regardless of whether any 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 must 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 in patients refractory to 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. Deferral of 14 days after first negative PCR is a minimum but should preferably be 21 days and a new PCR is recommended before the start of conditioning. It particular in patients with moderate to severe COVID-19 disease it 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. 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, 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. During the early phase of the pandemic, it was therefore strongly recommended to have secured stem cell product access by freezing the product before start of conditioning. Today several donor registries have returned to normal procedures and freezing of products are no longer the recommended procedure. Furthermore, there have been reports of poor stem cell yield after freezing and this will require further investigations. If there is concern that the donor is at high risk of community-acquired infection between work-up and collection, pre-planned cryopreservation will allow patient conditioning to be withheld until successful donation and delivery are confirmed. This has to be assessed on a case-by-case basis.

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.

In case of contact with a person diagnosed with SARS-CoV-2, the donor shall be excluded from donation for at least 28 days after the last contact. 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.

WMDA has produced recommendations and the EBMT endorses these guidelines. Please, refer to WMDA webpage (www.wmda.info) for updates.

DIAGNOSIS AND GENERAL MANAGEMENT OF COVID-19 PATIENTS

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. Co-pathogens should be evaluated and treated.

The long-term consequences of HCT patients who have had COVID-19 are still unknown. Other community-acquired respiratory viruses can cause late respiratory dysfunction in HCT recipients. It is therefore recommended to perform spirometry in HCT patients, who have resolved COVID-19. It is also important to be watchful for other late consequences that might occur.

TREATMENT OF COVID-19 POSITIVE HCT AND CAR T CELL PATIENTS

Antiviral drugs: 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. Remdesivir has been approved in the EU for treatment of severe COVID-19. One randomized clinical trial from China did not show improvement¹, 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%)². There was no difference in outcome between 5 and 10 days of treatment in patients with severe COVID-19³. A cohort study compared remdesivir with standard of care in patients with severe COVID-19 also showed improved resolution and lower mortality in remdesivir treated patients⁴. In a randomised patients with moderate COVID-19, there was no improvement in mortality between remdesivir treated patients and those receiving standard of care.⁵

Lopinavir/ritonavir has also been used but a published trial failed its primary endpoint^{6,7}. 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 alone⁸. Chloroquine and hydroxychloroquine have also been used with early data suggesting reduction of viral load⁹⁻¹³. 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 its use especially in outpatients. Currently evidence for the usefulness of these agents is weak and conflicting¹⁴. Hydroxychloroquine given as postexposure prophylaxis in a randomized trial did also not reduce the risk for COVID-19. Neither lopinavir/ritonavir or chloroquine/hydrochloroquine is currently recommended for treatment of COVID-19.

Convalescent plasma: Another option for COVID-19 treatment, if available, is convalescent plasma that has in non-controlled trials suggested some positive effect in a proportion of patients¹⁵. However, no randomized trial has been completed and reported. Interferon- α and - β are also being studied.

Anti-inflammatory treatment: Since an important part of the pathology seems to be cytokine release, different therapies addressing this syndrome have been tested. Short-term corticosteroid therapy was associated with lower mortality in immunocompetent patients with COVID-19 associated ARDS^{16,17} and has been shown to be effective in randomized trials and summarized in a metaanalysis¹⁸ and there is a WHO guideline regarding this treatment (WHO. Corticosteroids for COVID-19. Living guidance. 2 September 2020. WHO reference number: WHO/2019-nCoV/ Corticosteroids/20201.2020).

Tocilizumab, which is approved for cytokine release syndrome after CAR T cell therapy, have been used with promising results in non-randomized studies¹⁹. A randomized study, however,

failed to reach its primary endpoint (the COVACTA study; Roche press release July 29). Several other anti-inflammatory treatments are being studied.

Vaccination: Several vaccines are in development and it will be of uttermost importance to assess how these should be used in HCT recipients when they become available. Influenza vaccination is strongly recommended in HCT and CAR T cell treated patients.

Current status of therapeutic possibilities against COVID-19: At this point no clear recommendations can be made on specific therapies in HCT patients 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. Five days of remdesivir might provide benefit especially in HCT patients with moderate to severe COVID-19. Anti-inflammatory therapy with corticosteroids has been shown to be of value in non-transplant patients. Data regarding other anti-inflammatory therapies is conflicting.

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.

MAINTAINING QUALITY STANDARDS IN THE PANDEMIC: EBMT-JACIE SELF-ASSESSMENT

Since the start of the COVID-19 pandemic significant modifications to usual practice have been necessary within clinical, collection and processing facilities of HCT programs, alongside those in the broader healthcare organizations, including hospitals, transfusion services and public health. Adaptation of quality manuals, policies and procedures has been necessary to maintain quality of care and protect patients, donors and healthcare professionals to according to JACIE accreditation standards.

The EBMT-JACIE self-check offers HCT programmes a framework by which to assess and adapt their critical processes and services to minimise COVID-19 transmission and other risks within HCT programmes. These include COVID-19 minimised pathways for inpatient and outpatient patient care and support services (such as ITU), testing of patients, donors and staff

and modifications to laboratory processing practice (such as cryopreservation). With increased experience and evidence base, procedures to diagnose and treat HCT patients infected with COVID-19 should be progressively updated.

The checklist will not be formally assessed by JACIE but the submissions and certification can be made available for future inspections to assess crisis management and how centres responded. JACIE may aggregate anonymised responses into the survey data to analyse how centres are managing their processes during the restoration, recovery and re-surge phases of the COVID-19 pandemic. This will help inform future planning for delivery of JACIE accreditation throughout the ongoing pandemic. The self-assessment exercise has now been sent to all currently accredited centers but will shortly be opened to all EBMT member centres. Please contact jacie@ebmt.org for more information.

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