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 more than 46 million cases have been diagnosed worldwide. The pressure on the health care system during the spring was very high in Europe and many countries imposed major restrictions on meetings, travel, and everyday life. These restrictions resulted in a decline in the number of cases and therefore from the beginning of the summer 2020, restrictions were lifted in most European countries. However, during the fall the "2nd wave" has hit Europe with higher numbers of infected individuals than during the 1st wave although so far the number of severe cases needing ICU care and the number of deaths are also increasing.

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 are much lower 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 14th 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). Currently almost 500 patients have been registered from 22 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. Two new strains have emerged that might be spreading more rapidly although this is not clearly shown. 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 for a long time and it is 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. There are now different types of tests including PCR and rapid antigen detection tests. The latter are less sensitive; therefore, PCR tests remain as the recommended option in this document. The antigen tests have varying performance and can give both false negative and false positive results. The advantages are speed and the possibly to be used "point-of-care". Some authors therefore recommend that confirmatory testing with a nucleic acid amplification test (e.g., RT-PCR) should be considered after negative antigen test results in symptomatic persons and positive antigen test results in asymptomatic persons[1]. Therefore, PCR tests remain mandatory

for screening patients prior to admission to a transplant ward. However, antigen tests can have their place in emergency rooms and for screening of staff as long as the test has been evaluated and approved for the purpose by the proper national or regional authority. Return to work by staff members who have recovered from COVID-19 should follow national guidelines. Currently, there are no strong recommendations to regularly test asymptomatic healthcare workers. However, testing of an asymptomatic health care worker is recommended in case of contact with a suspected or documented case of proven SARS-CoV-2 infection.

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.

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 is then 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. 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. Patients should be adequately informed that the risk for severe complications is higher if the patient get infected with SARS-CoV-2 during or after the transplantation. 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. Patients, who have acquired COVID-19 immediately before HCT should be deferred due to the risk for progression to severe disease. The other situation is

patients, who have acquired COVID-19 some weeks before planned transplant and who are still PCR-positive but who either never developed symptoms or have resolved their symptoms. In the general population it is recognized that after 10 days from the onset of symptoms only few PCR positive patients can transmit a viable virus, and asymptomatic patients might be PCR positive for several weeks, alternating positive and negative PCR results. There have been reports of "viable SARS-CoV-2 for several weeks in patients, who are repeatedly PCR-positive[2]. This seems to be more common in immunosuppressed individuals. Furthermore, recurrence of symptoms when a patient became severely immunocompromised has been described and require new evaluation for COVID-19 but also for other respiratory viruses.

In general, if a transplant candidate is diagnosed with COVID-19, a deferral of the transplant procedure is recommended. 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. This is a difficult risk-benefit assessment and must be made individually with a complete information given to the patient about the risks for transplant complications vs. the risk for progression of the underlying disease. The decision must be made considering the risk of the patient associated with on one hand the delay of the procedure and on the other proceeding with conditioning and the risk for COVID-19 associated complications, especially pulmonary, as well as the risk for nosocomial spread of COVID-19 within a transplant unit.

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 is also important to take the severity of COVID-19 into account. 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, who were asymptomatic or only mildly symptomatic with upper respiratory tract symptoms, deferral of 14 days after first negative PCR is a minimum and a new PCR is recommended before the start of conditioning, while in patients with

moderate to severe COVID-19 disease, it is recommended to defer the transplantation for at least three months.

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. During the summer when the COVID-19 situation had become controlled several donor registries have returned to normal procedures and freezing of products are no longer the recommended procedure since there were also several reports of cryopreserved products never infused. The emergence of a new strain in the UK as well as another in South Africa has resulted in new travel restrictions and this increases most likely the need for cryopreservation.

Furthermore, there have been reports of poor stem cell yield after freezing and this will require further investigations. Many centers still, however, prefer to use cryopreserved pheresis products to ensure access to the product when the patient has been conditioned. If there is concern that the donor is at high risk of community-acquired infection between work-up and collection, pre-planned cryopreservation is recommended since it will allow patient conditioning to be withheld until successful donation and delivery are confirmed. Stem cell products can also be frozen at the collection site if there is a possibility of significant transport delay. It is more complicated to cryopreserve bone marrow so a change to peripheral blood stem cells should be considered if feasible.

In case of diagnosis of COVID-19, donor must be excluded from donation. It is currently unclear if G-CSF administration might carry an additional risk for the donor, but there have been reports of potential worsening of COVID-19 in patients in whom G-CSF was administered. Collection should be deferred for at least 14 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 donor contact with a person diagnosed with SARS-CoV-2, collection shall be deferred for at least 14 days after the last contact. The 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 14 days of donation should practice good hygiene and be as socially isolated as feasible during this period. Unnecessary travel should be avoided. It is recommended that donors are tested for COVID-19 so that results are available prior to their admission for the collection procedure, the staff of the pheresis unit and other donors and patients at the unit can be protected from an infected but asymptomatic donor.

WMDA has produced recommendations regarding unrelated donors and the EBMT endorses these guidelines. More details regarding recommendations for donor management during the COVID-19 pandemic can be found at their website. It should be recognized that the EBMT has to consider the situation in family donors such as children and elderly donors, who might be in a different situation than unrelated donors. The situation in many countries is likely to change rapidly over the near future and the function and recommendations from the individual registries can be accessed at: https://share.wmda.info/display/LP/COVID-19+-+Impact+on+Registry+Operations

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 since airborne transmission is increasingly becoming a concern[3]. 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: No antiviral drug has showed a significant impact in the death rate of COVID-19 [4].

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 improvement[5], 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 (11.4% vs. 15.2%) by day 29.[6] There was no difference in outcome between 5 and 10 days of treatment in patients with severe COVID-19.[7] 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 patients[8]. In a randomised patients with moderate COVID-19, there was no improvement in mortality between remdesivir treated patients and those receiving standard of care.[9] Interim results from the so called WHO Solidarity trial reported on hospitalized patients in 405 hospitals in 30 countries showed no or marginal benefit of remdesivir[10]. The combination of the data of 4 trials with remdesivir vs control [5,6,9,10], showed no significant impact in the death rate ratio (0.91, 95% CI 0.79-1.05)[10]. Based on these data, the WHO recently released a weak or conditional recommendation against the use of remdesivir in

hospitalized patients with COVID-19[4] as the evidence suggests no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes. However, this does not exclude that there might be a potential benefit in immunocompromised and other high-risk populations particularly in the early phase of the infection. The combination of remdesivir and baricitinib (a JAK 1 and 2 inhibitor) was in a randomized trial shown to be superior to remdesivir alone in reducing the time of recovery (primary endpoint) especially in patients receiving high-flow oxygen or non-invasive ventilation but did not improve survival[6].

Lopinavir/ritonavir has also been used but a published trial failed its primary endpoint[11,12]. 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 alone[13]. Chloroquine and hydroxychloroquine have also been used with early data suggesting reduction of viral load [14-18]. 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 conflicting[19]. In the WHO Solidarity trial[20], hydroxychloroquine, lopinavir/ritonavir and interferon did not definitely reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalisation duration. Hydroxychloroquine given as post- or pre-exposure prophylaxis in randomized trials did also not reduce the risk for COVID-19[21,22]. Neither lopinavir/ritonavir or chloroquine/ hydrochloroquine is currently recommended for treatment of COVID-19.

Convalescent plasma and monoclonal antibodies: Recently a monoclonal antibodies: bamlanivimab and a combination of casirivimab and imdevimab, received an emergency use authorization by the FDA for mild to moderate COVID-19 in non-hospitalized patients who are at risk for progressing to severe COVID-19. No data has so far been published and trials in hospitalized patients have been discontinued due to lack of efficacy.

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 patients[23]. Seven randomized trials have already been reported[24-27], three were terminated early, mostly due to falling local case numbers. Only one of these six trials, with only 21 patients, showed benefit

from convalescent plasma including a lower mortality. In the other 3 finalized randomized trials, convalescent plasma showed no benefit in patients with moderate[25] or severe COVID-19[24,28]. The 7th trial showed a significant reduction in the risk for progression to severe COVID-19 when older adults with mild COVID-19 were given high-titer convalescent plasma within 72 hours after onset of symptoms[27]. In a large observational study, no effect on mortality was observed in the overall population[29]. Nonetheless in a single arm study, convalescent plasma significantly reduced mortality in subgroups of patients: those who received convalescent plasma with higher vs. those with lower antibody levels, and those who received plasma within three days of COVID-19 diagnosis vs. those receiving it later.

Anti-inflammatory treatment: Since an important part of the pathology includes 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[30,31] and has been shown to be effective in randomized trials and summarized in a metaanalysis[32] 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, has been studied in five randomized studies in COVID19 patients. Four have been published [33-36], and one reported preliminarily (COVACTA; Rosas et al; medRxiv. 2020:2020.08.27.20183442). None had a significant impact on survival.

Vaccination will be covered in a separate guidelines document which can be accessed at https://www.ebmt.org/sites/default/files/2021-01/COVID%20vaccines%20version%203.04%20with%20table.pdf.pdf.

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 and data on their possible additive effects to corticosteroids is lacking.

Supportive care is crucial. Use of anti-coagulants to prevent thromboembolic complications, which can be frequent and severe in patients with COVID-19, have been shown to reduce mortality. Treatment of viral, bacterial, and fungal co-pathogens should be optimized. There is some information suggesting that individuals with low vitamin-D levels are more prone to develop more severe COVID-19 and it is therefore logical to supplement HCT individuals with vitamin D to achieve normal levels during the pandemic. 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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