



CORONAVIRUS DISEASE COVID-19: EBMT
RECOMMENDATIONS VERSION 17 – January 26, 2022

The Coronavirus Disease 2019 (COVID-19) pandemic is still highly active in many countries. In Europe, there is an ongoing 4th wave now with the Omicron variant despite high vaccination rates in many countries.

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, cancer, and pulmonary disease, are reported risk factors for severe disease and mortality.

Several mutated strains have emerged in different parts of the world (United Kingdom, California, South Africa, Brazil, India)¹. Some of these mutated variants spread more rapidly than the original type and has become the main variant detected in some countries. Currently available information suggest that different variants confer different risks for severe disease. Infections with the Delta variant have an increased risk for hospitalization and requirements of intensive care². The recently emerging Omicron variant, which now is rapidly spreading in the population, has been shown to cause infections also in completely vaccinated individuals and in individuals previously infected with other SARS-CoV-2 variants^{3,4}. There are reports showing that Omicron causes less serious disease in healthy individuals possibly due to lower propensity to infect the lower airways, but whether this is correct also in high-risk patients has yet to be ascertained (Wang et al; Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron; medRxiv: DOI: [10.1101/2021.12.30.21268495](https://doi.org/10.1101/2021.12.30.21268495)).

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 17th version of the guidelines, and we plan to continue to update them as deemed necessary.

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 (GETH). Currently more than 1350 patients have been registered and results from the 1st wave have been published in *Leukemia*⁵. The 6-week mortality in the 1st wave was approximately 25%. Preliminary data from the 2nd wave (August 1 – December 31 supports an improvement in outcome showing a mortality of a bit below 20%. However, the data has not yet been formally analyzed regarding distribution of risk factors. In a separate study performed together with the European Hematology Association, it was shown that the mortality among CAR T cell treated patients was 50%⁶. Vaccine breakthrough infections also occur and the mortality in a larger cohort of hematology patients was reported to be 12.4%⁷. A similar mortality is also found in a preliminary analysis of the EBMT registry data.

The data collection is ongoing, and we urge centers to continue to report their patients and send us follow-up information. We have updated the follow-up form to collect data also on vaccination and the new SARS-CoV-2 variants while deleting other variables to make the forms more up-to-date. Please, use this form available from the EBMT website (www.ebmt.org).

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, physical and social distancing, face mask use, especially for risk groups, are currently the main prevention strategies utilized in most European countries. After a period of lifted restrictions, the emergence and rapid spread of the Omicron variant have resulted in new restrictions in most European countries. Furthermore, it is now clear that Omicron can infect also individuals having received two

doses of vaccine and, however, probably to a lesser extent those who have received three doses.

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, especially with the Omicron variant. There are different types of tests including PCR and rapid antigen detection tests, both are highly specific⁸. The latter are less sensitive; therefore, PCR tests remain as the recommended option in this document. The advantages of antigen tests are speed and the possibility 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 persons⁹. 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.

Vaccinated health care staff has lower risk for carrying infectious virus, but a high level of caution is still recommended since the protection against infection and thereby the possibility for transmitting the virus is far from complete, especially not against the Omicron variant and it is increasing with time from the most recent vaccination. Return to work by staff members, who have tested positive for COVID-19 and who either are asymptomatic or have recovered, should follow national guidelines. 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. Regular screening is undertaken in many healthcare systems, and, where available, adherence to such policies should be encouraged to protect patients, even when staff are vaccinated. It should be recognized that the rapidly rising number of cases with the Omicron variant might result in changes in recommendations from different national authorities but considering the high risk for severe disease in HCT and CAR T cell treated patients, a high level of caution is strongly recommended.

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 strict visitor restrictions to transplant units even though they have been vaccinated. Testing, preferably by PCR, is still recommended if visitors are allowed into the transplantation unit.

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. Vaccination is covered by a separate part of these guidelines but it is recommended that vaccinated patients continue to follow guidelines aiming to decrease the risk of contracting SARS-CoV-2 especially early after transplantation and with ongoing immunosuppression or active GVHD.

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 gets 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. Furthermore, recurrence of symptoms when a patient became severely immunocompromised has been described. There have been reports of viable SARS-CoV-2 for several weeks or months in severely immunocompromised patients who are repeatedly PCR-positive. **This has made the USA CDC in their guidance regarding**

immunocompromised patients with COVID-19 to state that immunosuppressed individuals may produce replication-competent SARS-CoV-2 beyond 20 days and recommend a test-based strategy for management including two negative tests after resolution of symptoms for at least 24 hours and improvement of other symptoms and if a patient has been persistently PCR positive beyond 30 days consider additional testing (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html>)

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. Preliminary data from an EBMT registry study show a high risk for complications although the number of reported patients is too low to allow firm conclusions. The efficacy of monoclonal antibodies and antivirals in reducing the risk of progression to severe COVID-19 in this setting is unknown, but their use should be considered. It is important to take the severity of COVID-19 into account. In patients with moderate to severe COVID-19 disease it is 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, while in asymptomatic or mildly symptomatic patients, the risk for complications is likely relatively low when the patient is no longer PCR positive.

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. In patients with low-risk disease 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.

Stem cell products can be frozen either at the transplant center to ascertain that it is available when conditioning is started or at the collection site. It is more complicated to cryopreserve bone marrow so a change to peripheral blood stem cells should be considered if feasible. The emergence of the Omicron variant and its rapid spread in the population has resulted in centers reassessing the need for cryopreservation. Each center should address this issue on an individual basis.

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. Sequencing for mutated SARS-CoV-2 variants might be useful if such present in the surrounding community. 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 concern¹⁰. All patients positive for SARS-CoV-2 in an upper respiratory tract

sample should undergo evaluation of oxygenation impairment and chest imaging, preferably by CT, if signs of lower respiratory tract involvement is present. Routine bronchoalveolar lavage (BAL) is not recommended if a patient tested positive for SARS-CoV-2. Co-pathogens should be evaluated and treated.

In the general population, post-acute COVID-19 (long COVID) syndrome is well documented. While the definition of the post-acute COVID-19 is evolving, a recent interdisciplinary group defined it as persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms. It is further divided into two categories: (1) subacute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities present from 4–12 weeks beyond acute COVID-19; and (2) chronic or post-COVID-19 syndrome, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses¹¹. Particularly frequent are the pulmonary sequelae, seen in 40-65% of the cases. A reduction in diffusion capacity, the most commonly reported physiologic impairment in post-acute COVID-19, is related to the severity of acute illness. The frequency and severity of post-acute COVID-19 syndrome in HCT patients is still unknown. Studies to address this topic is being performed by the EBMT. 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 yet showed a significant impact in the death rate of COVID-19¹².

Remdesivir (Veklury, approved for patients 12 years of age and older and weighing at least 40 kg) 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 COVID-19 pneumonia that requires additional oxygen therapy. 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 remdesivir¹³. The combination of the data of 4 trials with remdesivir vs control showed no significant impact in the death rate ratio (0.91, 95% CI 0.79-1.05)¹³⁻¹⁶. Based on these data, the WHO released a weak or conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19 as

the evidence suggests no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes. Two systematic reviews have failed to show benefit of remdesivir treatment for COVID-19^{17,18}. 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 since treatment with remdesivir resulted in faster rates of recovery¹⁶. Additionally, 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 survival¹⁹. Recently, a short three-day course of remdesivir was shown to reduce the risk of progression to severe COVID-19 or hospitalization in symptomatic outpatients with COVID-19 (0.7% vs. 5.3%)²⁰

Two new oral drugs, molnupiravir (for patients of > 18 years) and ritonavir-boosted nirmatrelvir (Paxlovid, approved for patients 12 years of age and older weighing at least 40 kg) have received emergency use authorization by the FDA and several national authorities while EMA issued advice to support national authorities who may decide on possible early use prior to marketing authorisation. So far only limited data is available regarding the efficacy of these drugs especially in immunocompromised patients.

Molnupiravir is small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC) and an inhibitor of RNA-dependent RNA polymerase. Preliminary data from a trial including 1408 patients in adults with a prespecified chronic medical condition or an increased risk for severe SARS-CoV-2 infection has been presented and showed a 30% reduction in hospitalization or death (6.5% molnupiravir; 9.7% placebo) from COVID-19 infection²¹ (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain>). Side effects observed in the trial included diarrhea, nausea and dizziness. Due to the mechanism of action, molnupiravir induces errors in viral RNA, one concern is that it could theoretically speed up the evolution of the virus, particularly in immunocompromised patients.

Paxlovid consists of nirmatrelvir, which inhibits a SARS-CoV-2 protein to stop the virus from replicating, and ritonavir, which slows down nirmatrelvir's breakdown to help it remain in the body for a longer period at higher concentrations. Preliminary data from the phase III study including 2086 patients shows that Paxlovid significantly reduced the proportion of people with COVID-19 related hospitalization or death from any cause by 88% compared to placebo among patients treated within five days of symptom onset and

who did not receive COVID-19 therapeutic monoclonal antibody treatment. Mortality was 0.8% in Paxlovid treated and 6% in placebo treated patients. (<https://www.fda.gov/media/155050/download>). Side effects include taste disturbance, diarrhea, high blood pressure and muscle aches Paxlovid has important interactions with other drugs that need to be considered.

Thus, three antivirals have shown a substantial reduction in the risk of hospitalization in nonhospitalized patients (remdesivir, Paxlovid and in less grade molnupiravir)²². Close collaboration with specialists in infectious diseases is recommended to review therapeutic options.

Convalescent plasma and monoclonal antibodies: Several neutralizing IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2 are available for use within the EU such as bamlanivimab+etesevimab (for adults and children 12 years of age or older weighing at least 40 kg; this weight limit only applies to children), casirivimab+imdevimab (for adults and children aged 12 years and older weighing at least 40 kg), sotrovimab (for adults and children aged 12 years and older weighing at least 40 kg) or regdanvimab (for patients aged 12 years and older weighing at least 40 kg) and several others are being developed. Their use resulted in lower rate of hospital admission and SARS-CoV-2 infection progression in patients with mild to moderate COVID-19 who are non-hospitalized for COVID-19 but who are at risk for severe COVID-19²³⁻²⁶. The effect seems to be better in patients early in the course of the disease. It is likely that immunosuppressed individuals such as HCT or CAR T cell treated patients, who have lower capacity to mount strong immune responses, have increased benefit by the use of monoclonal antibodies.

A non-peer-reviewed report from the RECOVERY trial documented the benefit of high dose casirivimab + imdevimab in the subgroup of 3,153 hospital-admitted seronegative patients (day 28 mortality 24% vs. 30%, p=0.001), while no benefit was reported in seropositive patients (Horby et al, Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv. 2021:2021.06.15.21258542.)

However, the neutralizing capacity of most of these monoclonal antibodies, the exceptions being sotrovimab and AZD7442 (tixagevimab / cilgavimab, approved for

prophylaxis), against the Omicron variant is insufficient (<https://covdb.stanford.edu/page/susceptibility-data/>)²⁷.

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 patients²⁸. Eleven randomized trials have already been reported. A systematic review and quantitative analysis concluded that most studies were of poor quality but that there might be a place for convalescent plasma in critically ill patients or those mechanically ventilated and resistant to antiviral therapy and supportive care²⁹. Furthermore, also the neutralizing effect of hyperimmune plasma is reduced against the Omicron variant (<https://covdb.stanford.edu/page/susceptibility-data/>).

Of note, both types of passive antibody therapies may influence immune response to COVID-19 vaccines SARS-CoV-2. It is recommended to defer vaccination for at least 90 days as a precautionary measure to avoid potential interference of the antibody therapy with vaccine-induced immune responses.

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 metaanalysis³² 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).

Use of additional immunosuppressive agents has been recommended for the general population of patients with severe or critical COVID-19 (A living WHO guideline on drugs for covid-19 V.9.2 published January 14th 2022)

<https://app.magicapp.org/#/guideline/nBkO1E/rec/E5AOaN>

Tocilizumab, which is approved for cytokine release syndrome after CAR T cell therapy (for patients aged 2 years and older) has been studied in nine randomized studies in COVID19 patients. Two randomised trials have shown a survival benefit with the use of tocilizumab^{33,34}. In these two studies, nearly all patients received systemic corticosteroids (82% and 93%). The RECOVERY included 4,116 randomised patients. In the RECOVERY study, the use of tocilizumab in hospitalized COVID-19 patients with

hypoxia (oxygen saturation <92% on air) and systemic inflammation (C-reactive protein ≥ 75 mg/L), improved survival (rate ratio 0.85; 95% CI 0.76–0.94; $p=0.0028$) and other clinical outcomes (discharged from hospital within 28 days, less mechanical ventilation). These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids. In a meta-analysis of the other 8 randomized trials, tocilizumab was associated with a non-significant 11% reduction in mortality (rate ratio 0.89, 0.72–1.11). After inclusion of the results from the RECOVERY study into the meta-analysis, the mortality rate ratio from the nine trials was significantly reduced (rate ratio 0.86 (0.78–0.94, $p=0.0017$)). The use of systemic corticosteroid plus tocilizumab seems to reduce the mortality further. In the REMAP-CAP study, the use of tocilizumab or sarilumab in critically ill patients was associated with an improved survival at day 90 (HR 1.61, 95% credible interval, 1.25 to 2.08)³⁴. A recent Cochrane analysis concluded that tocilizumab reduced all-cause mortality in patients with COVID-19³⁵.

Sarilumab, another IL-6 blocker, has been also studied and can be used in this setting. Caution is advised when considering the use of IL-6 blockers in patients with a history of recurring or chronic infections and patients should be monitored for infectious complications.

Among Janus kinase (JAK) inhibitors, baricitinib is recommended as alternative to IL-6 blockers, based on preliminary data from the Recovery trial, while more data is needed for other JAK inhibitors such as ruxolitinib or tofacitinib. (A living WHO guideline on drugs for covid-19 V.9.2 published January 14th 2022)

<https://app.magicapp.org/#/guideline/nBkO1E/rec/E5AOaN>

Anakinra (Kineret, authorized for patients aged 8 months and older) is a recombinant human IL-1 receptor antagonist and was recently approved by the EMA for treatment of COVID-19 in adults with pneumonia requiring supplemental oxygen (low or high flow oxygen) and who are at risk of developing severe respiratory failure, as determined by blood levels of suPAR (soluble urokinase plasminogen activator receptor). Results from the randomized SAVE-MORE study showed that early, urokinase plasminogen receptor guided treatment with IL-1 receptor antagonist anakinra reduced the mortality, ICU admission and increased the likelihood of full recovery in 594 patients with moderate/severe COVID-19 pneumonia³⁶.

Three randomized trials, one with more than 4000 patients showed a positive effect of colchicine in COVID-19 clinical outcome with a 20% decrease of death/hospitalization for

COVID-19 in non-hospitalized patients³⁷. A recent meta-analysis confirmed the reduction in mortality by colchicine³⁸.

Another potential strategy to treat COVID-19 is the use of antibodies targeting GM-CSF. Preliminary data from a randomized, double-blind, placebo-controlled trial showed that lenzilumab improved “survival without ventilation” in hospitalized patients with COVID-19³⁹. On the other hand, another antibody targeting GM-CSF (mavrilimumab) failed in a small, randomized trial to improve outcome⁴⁰. Additional studies are needed.

Vaccination is covered in a separate guidelines document (<https://www.ebmt.org/covid-19-and-bmt>).

Current status of therapeutic possibilities against COVID-19: Current status of therapeutic possibilities against COVID-19: There is support for use of monoclonal antibodies in selected patients particularly early during the infection. The effect of most monoclonal antibodies, however, is insufficient against the Omicron variant so sotrovimab is currently the only option for early treatment in such cases. Other new options for early treatment of mild/moderate SARS-CoV-2 infection with the aim of preventing severe COVID-19 and/or hospitalisation are oral antivirals such as molnupiravir (Lagevrio) and ritonavir-boosted nirmatrelvir (Paxlovid) or 3-day intravenous treatment with remdesivir. Therapy should be given in close collaboration with specialists in infectious diseases.

Anti-inflammatory therapy with corticosteroids has been shown to be of value in non-transplant patients. The use of a second immunosuppressant, mainly tocilizumab, combined with systemic corticosteroids increase survival in patients with severe or critical COVID-19.

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.

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CORONAVIRUS DISEASE COVID-19: EBMT RECOMMENDATIONS

[VERSION 17– January 26, 2022](#)

Table 1.

Summary of EBMT RECOMMENDATIONS for SARS-CoV-2

General considerations
<ul style="list-style-type: none">• 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• All patients including those vaccinated should continue to follow these procedures to limit the risk for contracting SARS-CoV-2.• Correct selection of the mask and correct use are crucial (see text)• Sequencing for mutated SARS-CoV-2 variants should be considered
Healthcare workers
<ul style="list-style-type: none">• Staff with any symptoms of infection should stay at home<ul style="list-style-type: none">○ Testing for SARS-CoV-2 is strongly recommended since symptoms can be uncharacteristic and very mild. PCR is the test recommended in this document. However, antigen tests can have their place in screening of staff before work 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, usually requiring the resolution of symptoms and two negative PCR results.• Testing asymptomatic healthcare workers: there are no general recommendations to regularly test asymptomatic healthcare workers. Nonetheless, Regular screening is undertaken in many healthcare systems, and, where available, adherence to such policies should be encouraged to protect patients, even when staff are vaccinated• 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.• Staff should preferably be dedicated to a COVID-19 free transplant unit and not used interchangeably to care for COVID-19 positive patients.
Outpatient visits and visitors
<ul style="list-style-type: none">• 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.• Visitor to transplant units. When there is substantial COVID-19 activity, it is recommended to maintain visitor restrictions to transplant units<ul style="list-style-type: none">○ 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

Transplant patients

- **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 that become infected by SARS-CoV-2**
 - 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 (see text)
 - The decision to defer or not the transplant must be made taking into account several factors (see text)
 - 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
 - **In patients with high-risk disease**
 - SCT should be deferred until the patient is asymptomatic and has two negative virus PCR swabs taken at least 24 hours apart
 - **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 the conditioning.
 - for those 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
- **Before starting the transplant procedure**
 - Patients should be adequately informed that the risk for severe complications can be higher if the patient get infected with SARS-CoV-2 during or after the transplantation
 - Availability of adequately trained staff, ICU beds, ventilators, as well as availability of the stem cell product should be ensured
 - 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
 - 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
- **Patients after HCT or CAR T cell therapy.**
 - Those 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
 - refrain from travel and if travel is deemed necessary, travel by private car instead of any public transportations system 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

Donors

- **WMDA** has produced recommendations regarding unrelated donors and the EBMT endorses these guidelines. It should be recognized that the EBMT has to consider family donors such as children and elderly donors, who might be in a different situation than unrelated donors.
- **Social isolation before donation:** 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
- **Donors with close contact or diagnosed with COVID-19**
 - **Diagnosed with COVID-19:** Collection should be deferred for at least 14 days after recovery
 - **In case of close contact with a person diagnosed with COVID:** the donor shall be excluded from donation for at least 28 days after the last contact
 - **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
- **Testing before collection**
 - It is recommended that donors are tested for COVID-19 and that results are available prior to starting the collection procedure, in order to protect the staff of the pheresis unit and other patients that can be at the unit at the same time from an infected donor
- **Cryopreservation of stem cells**
 - 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 harvest site if prolonged transport time is expected

DIAGNOSIS AND GENERAL MANAGEMENT OF COVID-19 PATIENTS

- **Diagnostic procedures for COVID-19**
 - Should follow national or local guidelines
 - 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
 - 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.
 - It is recommended to perform spirometry in HCT patients, who have resolved COVID-19

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

- Supportive care is crucial especially anti-coagulants to prevent thrombo-embolic events.
- Co-pathogens should be evaluated and treated
- **Close collaboration with specialists in infectious disease is recommended to discuss therapeutic options.**
- **Antiviral drugs**
 - No antiviral drug has showed a significant impact in the death rate of COVID-19
 - Remdesivir has been approved in the EU for treatment of severe COVID-19
 - Recently a short three day course of remdesivir was shown to reduce the risk for progression to severe disease or the requirement of hospitalization
 - Two new drugs, molnupiravir and Paxlovid are being introduced having shown efficacy in reducing the risk for progression to severe COVID-19 disease.
- **Convalescent plasma and monoclonal antibodies:**
 - **Monoclonal antibodies**
 - Recently several monoclonal antibodies against COVID-19 have become available for treatment of non-severe COVID-19
 - There is support for their use particularly early during the infection.
 - Most monoclonal antibodies (the exception being sotrovimab and the combination of tixagevimab/cilgavimab; the latter used for prophylaxis) have decreased neutralizing capacity against the Omicron variant.
 - **Convalescent plasma**
 - In randomised trials no effect on mortality was observed.
 - if monoclonal antibodies are not available, high titre convalescent plasma might be of benefit in seronegative immunocompromised patients, particularly if administered early during the infection
 - However, the neutralizing effect is reduced against the Omicron variant

Antiinflammatory therapy

- **Corticosteroids**
 - Short-term corticosteroid therapy (7-10 days) was associated with lower mortality in immunocompetent patients with severe and critical COVID-19, was shown to be effective in randomized trials and is endorsed by the WHO guideline.
- **Tocilizumab:**
 - Meta-analysis of randomized, controlled trials supports a reduction of all-cause mortality.
 - In two large, randomized trials, the use of tocilizumab combined with systemic corticosteroids increase survival in hospitalized COVID-19 patients with hypoxia and systemic inflammation, and in critically ill patients
- **Sarilumab**
 - This anti IL-6 blocker can also be used in this setting
- Colchicine. A recent meta-analysis showed a reduction in mortality
- **Anakinra** guided by Urokinase Plasminogen Receptor, seems to improve clinical outcome, including reduced mortality, in patients with moderate/severe COVID-19 pneumonia