

BSBMT&CT recommendations for the management of adult patients and allogeneic donors during the COVID-19 (causative agent the SARS-CoV-2 virus) outbreak.

Since the introduction of the 'lock-down' request by the government the peak incidence of COVID-19 has been reached with a decline in cases from late April. It is now likely that the country will enter into a period of steady-state incidence but with the possibility of a second rise in cases once the lock-down is relaxed. Whatever the outcome, the SARS-CoV-2 virus will remain prevalent in the community posing a continuous risk to HSC transplant patients. These recommendations are intended to help transplant teams adapt to the presence of the risk and to continue to perform transplant procedures, autologous and allogeneic, keeping risks of COVID-19 at a minimum.

The recommendation to reduce transplant activity at the onset of the pandemic was based on two concerns;

- 1) **Capacity:** The capacity within transplant centres to manage patients, bed capacity in the units, ICU bed availability and staffing reduction due to illness, self-isolation and transfer to non-transplant activities.
- 2) **COVID-19 risk:** The risk of COVID-19 in this vulnerable patient group.

Capacity problems have varied across the country with some centres, particularly those in London and the Midlands, experiencing severe pressures with other centres less affected. Recovery of transplant activity will depend on the local availability of bed capacity and staffing levels. Although capacity pressures will reduce the risk from COVID-19 will remain for some time, it is this risk that transplant teams will need to address before beginning the recovery of transplant activity.

The following recommendations are based on the guidance obtained from several sources including the EBMT, ASTCT, WMDA, Anthony Nolan and NHSBT. More importantly it represents a consensus from UK transplant teams and disease groups. Individual centres should use these recommendations for general guidance only as circumstances will vary from centre to centre and institutional procedures should be followed. These recommendations have been produced in order to provide support to BMT teams in the UK. Advice may change as the COVID-19 prevalence changes in the UK.

Transplant teams are advised to carefully read the latest guidance from the EBMT, ASTCT and for donor issues, the Anthony Nolan and NHSBT.

EBMT guidance, updated April 7th 2020:

https://www.ebmt.org/sites/default/files/2020-04/EBMT-COVID-19-guidelines_v.6.1%282020-04-07%29.pdf

ASTCT guidance, current version 1.3 April 16th 2020:

[https://higherlogicdownload.s3.amazonaws.com/ASBMT/a1e2ac9a-36d2-4e23-945c-45118b667268/UploadedImages/COVID-19 Interim Patient Guidelines 4 20 20.pdf](https://higherlogicdownload.s3.amazonaws.com/ASBMT/a1e2ac9a-36d2-4e23-945c-45118b667268/UploadedImages/COVID-19%20Interim%20Patient%20Guidelines%204%202020.pdf)

WMDA weblink:

<https://share.wmda.info/display/LP/COVID-19+-+Impact+on+Registry+Operations#/>

Anthony Nolan COVID-19 link, updated 29th April 2020:

<https://www.anthonynolan.org/patients-and-families/understanding-stem-cell-transplants/coronavirus-and-your-stem-cell-transplant>

NHSBT link:

<https://www.nhsbt.nhs.uk/news/coronavirus-update/>

NICE Guideline NG164, 1st April 2020 - COVID-19 rapid guideline: haematopoietic stem cell transplantation

<https://www.nice.org.uk/guidance/ng164>

UK Myeloma Forum COVID-19 Guidelines:

<https://www.ukmf.org.uk/guidelines/covid-19-guidance/>

BSBMT&CT Collaborative Group advice.

Changes since the last set of recommendations:

- 1) Addition of recommendations for recovery planning.
- 2) Updated links to other HSCT organisations.
- 3) Update of BSBMTCT transplant priorities table.
- 4) Clarification regarding period of shielding and social behaviour intended to reduce infection risks.

Recovery preparations:

It is advised for programs to gradually restart transplant activity taking into consideration local capacity, case prioritisation, establishing safe patient treatment pathways and robust SARS-CoV-2 surveillance procedures.

The main patient groups that have been affected by the deferral of transplantation are those requiring autologous HSCT for myeloma and lymphoma. The BSBMTCT have worked closely with the UK Myeloma Forum in preparing the recovery recommendations.

Capacity

- It is essential that centres are able to confirm sufficient capacity to manage planned activity. This includes:
 - Bed capacity in the transplant unit and ICU.
 - Staffing on BMT unit. Repatriation of staff if reallocated at the start of the crisis.
 - Stem cell laboratory capacity to manage donor cells for cryopreservation.
 - Associated services – pharmacy, renal support, physiotherapy.
 - Laboratory testing for SARS-CoV-2 in patients and staff.
 - Safe access to critical investigations such as endoscopy, bronchoscopy
- Establish 'COVID-19 safe' patient treatment pathways, from clinics, during in-patient stay and post-transplant care. How this will be achieved will depend on the circumstances in each transplant centre, in some cases restarting transplant activity may not be possible and the NHSE BMT regional networks may be required to allow patients to be transferred to nearby centres that are able to provide COVID-19 safe care.
- Gradual recovery plan with small numbers of patients initially from waiting lists.
- Continued suspension of ambulatory transplant operations unless the risks of frequent hospital visits can be mitigated by patient benefit; the decision should be patient-focussed and ratified by the relevant MDT.

Case selection

As patients are deferred the balance of risks from COVID-19 infection and the delay to proceeding with transplantation begins to change. It is recommended that every case is assessed by local teams at MDTs. The priorities table remains a useful tool, patients deferred at the onset of the pandemic may now be considered to be in the clinical high risk category. Case-by-case decision making will be essential to safe re-starting of transplant activity.

- Continue to follow NICE Rapid Guideline for COVID-19 in HSCT for guidance with prioritisation for patients with high risk disease based on disease characteristics and period of deferral.
- Refer to disease specific professional groups for guidance.
- Case-by-case decisions based on MDT discussions.
- Continue to cryopreserve sibling and allogeneic donor cells prior to the start of conditioning.
- Consult disease specific organisations which may provide guidelines to inform MDT decisions

SARS-CoV-2 surveillance

It will be important to develop and maintain robust policies and procedures to protect HSCT patients from SARS-CoV-2. These should be incorporated into existing Quality Management plans. The virus will remain within the community and will continue to be a major risk to patients indefinitely. Programs must work with their local infectious diseases and infection control teams to create safe operational environments for patients. How this will be achieved will have to be determined at a local level but policies that include regular staff screening by symptom awareness, viral swab tests, serology to determine immunity are likely to be required.

- Screening protocols – symptoms, naso-pharyngeal and throat swabs, serology (when available).
- Screening of BMT unit staff and in-patients with viral swabs at a minimum on a weekly basis.
- Pre-admission screening by symptoms checks and viral swabs, ideally within 72hrs of planned admission
- Patient triage and quarantine policies in clinics, in hospital, in ambulatory treatment pathways.

Prophylaxis and treatment:

Transplant units will be familiar with the prevention and spread of respiratory viruses within their programs. It is vital that programs continue to review their existing respiratory pathogen management procedures, policies and, for the current outbreak, align with local hospital and national policies and procedures. Patients at any time during their transplant pathway should be screened for possible upper respiratory tract infections (URTI) by careful history taking, particularly paying attention to respiratory symptoms, fevers, cough, shortness of breath. SARS-CoV-2 appears to mainly cause fever, dry cough and sore throat with coryza occurring in only a minority of cases but other symptoms may occur. Any patient pre, peri or post-transplant with respiratory symptoms should be isolated and tested for respiratory viral pathogens including but not only SARS-CoV-2 by nasal and throat swabs for PCR. Local guidelines must be followed for any patients identified as positive for SARS-CoV-2. Note that other respiratory viral pathogens are already known to be a serious risk to transplant recipients and if identified during screening appropriate measures should be taken including deferral of transplantation.

It is very important that staff responsible for taking viral swabs follow correct procedures to avoid false negative results. Recommend formal training and documented evidence of correct technique, ideally as part of the JACIE quality management system within the transplant program.

At this time there are no proven effective anti-viral agents recommended specifically for SARS-CoV-2, however anti-microbial therapy should be optimised with treatment directed according to any positive isolates. There is emerging evidence that part of the COVID-19 pathology is due to an inflammatory response to the virus that occurs 5-7 days following the appearance of symptoms. Several potential anti-inflammatory agents are under investigation and may be recommended in the future. See section on the COVID-19 Therapeutics Advice & Support Group (CTAG) at the end of this document. When possible COVID-19 patients should be entered into clinical trials.

Pre-SCT:

- As a preventative measure patients should be advised to avoid crowded places, public transport, use good hand hygiene measures and remain in self-isolation for 14 days prior to the start of conditioning.
- Careful history taking to determine whether the patient has had a recent contact with an individual proven to have COVID-19 or symptoms suggestive of COVID-19 (see PHE website). Travel to high risk countries has become a redundant screening tool.
- Any planned transplant should be reviewed and deferred if possible following the NICE Rapid Guidance. A phased recovery of transplant activity may be possible for centres that have prepared with policies and procedures in place to minimise risks from COVID-19.

All patients should be tested for SARS-CoV-2 by nasal and throat swabs by PCR before starting conditioning, as there is an asymptomatic period testing should be repeated at least twice, 1 week apart, but practice and availability of testing may vary between institutions. However it would be vital to test transplant patients prior to the start of conditioning if they have a history of recent contact with symptomatic individuals.

Psychological and emotional support:

Patients will be under considerable additional psychological and emotional stress due to the risks associated with COVID-19. Ensure that sufficient support processes and staff are available to provide support for patients and their families.

The following table may help in determining transplant prioritisation:

Priority level	Categorisation based on treatment intent and risk:benefit ratio of treatment
1	<p>Urgent allogeneic HSCT if delaying the procedure presents a high risk of disease progression, morbidity or mortality. This will mainly be malignant cases with a small number of urgent, non-malignant conditions.</p> <ul style="list-style-type: none"> • High cure fraction or other clinical and long term effectiveness
2	<p>HSCT procedures where there is risk of disease progression or clinical complications if delayed significantly (e.g. > 6 months)</p> <ul style="list-style-type: none"> • Intermediate cure fraction or effectiveness <p>For example: High-grade lymphomas and other urgent cases needing autologous HSCT for curative intent (for example diffuse large B-cell lymphoma and Hodgkin lymphomas) based on clinical risk assessment. Myeloma cases identified as clinical high risk due to disease characteristics or prolonged deferral.</p>
3	<p>HSCT procedures where the risk of disease progression or clinical complications if significantly delayed is low (e.g. over 6 months). This group also includes:</p> <ul style="list-style-type: none"> • procedures where the risks associated with undertaking an HSCT procedure within the current environment are deemed to be higher than the benefits of the procedure • procedures that are not of curative intent or limited long-term effectiveness <p>For example: Chronic conditions including most non-malignant indications and low-risk malignant indications for allogeneic HSCT (most should be deferred until the risks associated with the COVID-19 pandemic have passed). Allogeneic HSCT recipients with relatively low predicted survival; for example, 20 to 30% at 5 yrs based on pre-HSCT characteristics; all but exceptional cases should be deferred until the risks associated with the COVID-19 pandemic have passed. Autologous HSCT for myeloma, low-grade lymphoproliferative diseases and non-malignant indications; all but exceptional cases should be deferred until the risks associated with the COVID-19 pandemic have passed.</p>

Advise using transplant outcome predictive tools such as the refined disease risk index¹ and HCT-CI² (link to on line calculator at [HCT-CI](#)) to inform decision-making for patients.

SARS-CoV-2 positive patients:

Any patients testing positive for SARS-CoV-2 prior to SCT should be delayed by at least 3 months (ECDC recommendations), however this is not always possible due to the risk from the underlying disease. Therefore, in patients with high risk disease, HCT should be deferred until the patient is asymptomatic and has achieved three virus PCR negative tests at least one week apart (deferral of 14 days minimum). In patients with low risk disease a three-month HCT deferral is recommended.

Autologous transplant recipients

- Programs should plan for restarting autologous transplantation as detailed in the preceding sections.
- Advice will be continue to be produced by the disease specific specialist groups, UK Myeloma Forum and Lymphoma Specialist Interest Group.
- Decisions on which patients to prioritise should be based on clinical risk assessments, decided in MDT settings.
- Asymptomatic recipients should be screened for respiratory viruses and SARs-CoV-2 at least once 72 hrs prior to the start of conditioning.
- If clinically appropriate, GCSF alone mobilisation should be used.
- If chemotherapy priming or GCSF alone, test by SARS-CoV-19 swabs *prior* to start of treatment.
- Autologous donors *do not* require repeated SARS-CoV-19 testing on the day of stem cell harvest.
- Autologous SCT for non-malignant indications should be deferred until the peak of COVID-19 passes. Continued suspension of ambulatory transplant operations unless the risks of frequent hospital visits can be mitigated by patient benefit and the decision should be patient-focussed and ratified by the relevant MDT.

Allogeneic transplant recipients

- Careful planning required for the preparative regimen as the need to cryopreserve donor cells prior to starting condition may continue (see donor section).
- Asymptomatic recipients should be screened for respiratory viruses and SARs-CoV-2 at least once 72 hrs prior to the start of conditioning.
- Defer transplantation for any non-urgent indications. This will require allo-SCT MDT discussion on a case by case basis. Examples would be for MDS, MPD.
- Patients and relatives should receive instructions regarding isolation and preventative measures, this should be repeated and supported with written information.
- If close contact with COVID-19 individual immediately prior to transplant defer transplant for 3 weeks if possible (EBMT guidelines), test if symptomatic following local infection control guidelines.
- Patients who test +ve pre-SCT should be deferred where possible by at least 3 months until asymptomatic with viral throat swab negative x 3 tests, 1 week apart (EBMT guidelines). In patients with high risk disease HCT should be deferred until the patient is asymptomatic and has achieved three virus PCR negative tests at least one week apart (deferral of 14 days minimum).

Allogeneic donors

- Advise sibling donors to avoid crowded public places, practise good hygiene and avoid large group gatherings for 28 days prior to donation (EBMT Guidelines). Note this is not as strict as the self-isolation recommended recipients for 14 days prior to HSCT.
- Screen by viral swabs donors if symptomatic. If asymptomatic, screen as indicated below.
- Recommend harvesting sibling and cryopreserving stem cells prior to conditioning.
- Anthony Nolan now strongly recommend moving to shipping and cryopreserving stem cells before starting conditioning because of the risk of donor becoming ill and being unfit to donate plus growing uncertainties regarding transport. Liaise with local processing laboratories to warn them of each donation and whether to cryopreserve or not.
- Anthony Nolan will arrange SARS-CoV-2 testing of donor at the medical and repeated on the first day of harvest. Results should be available by the time product is cryopreserved. If not the processing laboratory may need to quarantine cryopreserved cells until results available.
- Sibling donors should also be screened twice, once at the medical prior to start of GCSF and again on the first day of harvest.
- Donors will be excluded from donation for 3 months if proven COVID-19 or for 4 weeks if in close contact with COVID-19 case (EBMT recommendations). Screening for SARS-CoV-2 will be required. If no suitable alternate donors and SCT urgent, perform risk assessment and lease with registry. In this situation the recipient should be involved in the discussion and be informed of the donor situation.
- Identify back-up donor from different country or cord in case harvesting/transport of 1st donor problematic (Anthony Nolan will facilitate).
- Consider the option of a haplo-identical donor as a back-up.
- There have been concerns that SARS-CoV-2 may be passed via blood products. Although viral RNA has been detected in blood samples of patients with COVID-19 there have been no reports of transmission of infection by blood products.

- Advise avoiding bone marrow as the stem cell source as access to theatres may be limited and prone to sudden cancellation depending on local circumstances.
- Donors should be contacted approximately 14 days post-harvest to determine if they have experienced any symptoms suggestive of COVID-19.

Peri and Post-transplant:

- Minimise the number of family members that visit patients, ideally none except in exceptional circumstances.
- Educate all family members on hand hygiene, and how to avoid potential contact risk behaviour.
- Patients should be managed in strict protective isolation; risk assess the need for any investigations and procedures that remove the patient from their isolation room, there may be a greater risk from exposure to SARS-CoV-2 than from not having the investigation.
- Patients who are known to be SARS-CoV-2 +ve should be isolated in negative pressure cubicles wherever possible, failing this in a neutral pressure cubicle. When seeing such patients, healthcare professionals should wear full PPE including gowns, FFP3 masks, gloves and visors.
- In order to establish COVID-19 free environments and the evidence of asymptomatic carriage and possible transmission it is will be necessary to screen ward staff routinely in contact with patients. Regular screening of in-patients is also recommended. This will depend on local availability of testing but programs should work with their Infection Control and Infectious Disease teams to develop routine procedures.

After discharge:

- **This will be the time of greatest risk to transplant recipients.**
- At discharge reinforce need for shielding of the transplant recipient and if possible the immediate carer.

PHE recommendations for shielding (high degree of isolation for 12 weeks or until end of June '20):

- These apply to autologous SCT recipients who have received an autoSCT *within* the previous 12 months.
- These apply to allogeneic SCT recipients who have received an allo-SCT *within* the previous 2 yrs or for patients with continuing immunosuppressive therapy, chronic GvHD or ongoing evidence of immunodeficiency based on insufficient CD4 count and/or hypogammaglobulinaemia.
- For newly transplanted patients, the period of shielding starts *from the time of discharge* for 12 weeks.

After the period of shielding patients should follow social distancing behaviour to minimise the risks of viral infections*.

- Minimise clinic visits, review how patients travel to the centre and try to reduce risks from public transport. Hospital transport may become limited.
- Set up telephone or video follow-up clinics, explore ways for patients to have blood tests away from busy areas in hospitals.
- As some patients will still require face-to-face visits for review centres must develop strategies to minimise risks to patients attending the hospital.

Staff:

- Healthcare professionals with cough/SOB/fever should not come to work.
- Be aware of the less frequent symptoms that have been associated with SARS-CoV-2 infection, staff education and self-reporting procedures must be in place to increase awareness of these symptoms.
- HCP who are coryzal without fever should avoid coming to work and self-isolate for at least 7 days. They should be screened for respiratory viruses and SARS-CoV-2. These recommendations need to be discussed with your local Infection Control Team.
- There is evidence that healthy individuals can continue to shed virus for up to 12 days from the onset of symptoms. Therefore staff should be *symptom free for 7 days and* have a *negative viral swab* before working directly with patients, consistent with NICE Guidelines.
- Switch meetings/MDTs to telecons as much as possible and if possible splitting workforce to mitigate risk of large proportion of team being affected at same time
- Avoid work related international travel/ large meetings
- Be aware of the additional psychological and emotional stress that staff will experience and identify measures to provide support.

CAR-T therapy:

As yet no clear consensus. Patients are at increased risk peri- and post-treatment. Additional risk from interruptions in the manufacturing chain. The pharmaceutical companies involved in the manufacture of CAR-T should be contacted directly for up to date information.

CTAG

COVID-19 Therapeutics Advice & Support Group (CTAG) was established through discussion between Drugs and Therapeutics Committees (DTCs) and specialists to provide advice and support in the management of COVID-19 whilst national guidelines evolve. CTAG primarily draws on advice from national sources (NHSE, MHRA, NIHR, CMO's office) and uses published literature with expert opinion when necessary. CTAG's outputs take the format of 'Position Statements'. Two priority statements have been developed:

- *Antivirals* <https://ctag-support.org.uk/docs/antivirals.pdf>
- *Immunomodulatory agents* <https://ctag-support.org.uk/docs/immunomodulators.pdf>

These may be of use in patients with evidence of COVID-19 related secondary HLH.

Continue to check the most up to date guidelines from the donor registries, disease specific groups and EBMT.

BSBMTCT Executive

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Refs:

1. Armand P et al, Blood 2014; 123:3664-3671
2. Sorror M et al, J Clin Onc 2014; 32:3249-3256

*Social distancing behaviour examples:

- Avoid contact with someone who is displaying symptoms of coronavirus (COVID-19). These symptoms include high temperature, new and continuous cough, shortness of breath.
- Work from home where possible.
- Avoid non-essential use of public transport, varying your travel times to avoid rush hour, when possible.
- Avoid large gatherings, and gatherings in smaller public spaces such as pubs, cinemas, restaurants, theatres, bars, clubs when these re-open.
- Avoid gatherings with friends and family. If they do need to visit, be extra cautious about hygiene, touching and hand-washing. Keep in contact using remote technology such as phone, internet, and social media.