

COVID-19 & allogeneic transplant: Activity and preventive measures for best outcomes in China

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1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly transmissible viral illness caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). This virus triggered a pandemic crisis for health care systems worldwide. Initial experience from China indicated that patients with cancer had a higher risk of COVID-19 infection and poorer outcomes after developing COVID-19 than individuals without cancer.¹ Patients with hematologic malignancy or receiving transplantation are immunosuppressed and may be particularly vulnerable to viral infections, and the hematology community faces unprecedented challenges.

The rapidly expanding COVID-19 pandemic has affected all aspects of medical activity, including hematopoietic stem cell transplantation (HSCT). Based on our current experience, preventive work of novel coronavirus is extremely important to mitigate its impact. Outside the epicentre (Wuhan), transplantation activity in China was not halted. We recommend preservation of transplantation activity under the premise of ensuring safety. This comment describes the possible impact of the current COVID-19 pandemic on transplantation activity and introduces interim precautions in our centre during the outbreak period.

2 | TRANSPLANTATION ACTIVITY DURING THE PANDEMIC IN CHINA

2.1 | Current challenges and situation of transplantation

Although transplantation activity in China was not interrupted during the viral pandemic, huge challenges remain and must be addressed.

Many patients may suffer from postponed transplantation to varying degrees due to the strict screening of donors and recipients and a shortage of blood products and isolation beds. Blood products shortage has already become a global problem because volunteer donors are obviously decreased as a result of self-isolation, travel restriction and fear of virus transmission.²

As suggested by ASH Q&A, decisions on whether to postpone transplantation must be made on a patient-by-patient basis.³ Diseases should be evaluated and classified, and priority should be given to urgent cases with high risk of relapse. For nonurgent cases, appropriate delay is allowed after balancing the deferred time of transplantation with the risk of disease relapse. To reduce the risk of relapse before transplantation, targeted therapeutic drugs for primary diseases may be used, and if there are no targeted drugs, low-dose chemotherapy may be administered for maintenance treatment.

2.2 | Present changes in transplantation procedures

Szer et al recently demonstrated the impact of COVID-19 on the provision of donor hematopoietic stem cell products worldwide. The report suggests preemptive cryopreservation of products to minimize the impact of the outbreak on transport difficulties and ensure the safety of cell products before infusion.⁴ This recommendation is consistent with updated EBMT recommendations in 2020, which strongly recommends to secure stem cell products by freezing the cells before the start of conditioning.⁵ Another concern is that cells stored frozen in a cryopreserved state may already be infected with COVID-19. Therefore, a reliable test for screening COVID-19 is essential before the cells are stored and used clinically.

Due to easy availability and rapid access, haploidentical donors were used far more than unrelated donors in recent years in China.⁶ Haploidentical donors achieve comparable outcomes with matched sibling donors.⁷⁻⁹ Besides, there are several specific characteristics of unrelated donors in China, including the low probability of finding an appropriate donor (appropriately 11%), long periods required for searching (3-6 months), possible situation of donors opting out of donation at any time, and little chance of re-donation if necessary.¹⁰

During the outbreak of COVID-19, haploidentical donors had more advantages over unrelated donors because they are less affected under these rapidly changing conditions. First, not only 1 haploidentical donor is feasible because a back-up haploidentical donor is always available for most patients. Second, family members have similar activity trajectories as patients, which is beneficial for confirming the travel or contact history of donors. Finally, The Data Bank of Chinese Hematopoietic Stem Cell Donors also strengthens the management of unrelated donor cell collection, transportation and infusion, which leads to a more complicated process because of COVID-19.¹¹

As for graft composition in the Beijing Protocol, fresh bone marrow combined with peripheral blood stem cells (PBSCs) are routinely recommended for inducing immune tolerance.¹² As advocated by the National Health Commission, selective surgeries are restrictive to reduce the risk of cross-infection in the operating room during the outbreak. The feasibility, effectiveness, and tolerability of PBSCs as a graft source were also verified in unmanipulated haploidentical transplantation.¹³ Therefore, we advocated for fresh PBSCs as the only graft source during this special period.

3 | PREVENTION IS THE KEY STEP FOR ENSURING FEASIBLE TRANSPLANTATION

3.1 | Strict screening of recipients and donors

The donor and recipient must be healthy for HSCT to be feasible and successful. Therefore, we first emphasize the importance of meticulous screening of donors and patients.

Donors should be screened for the following items. Prior to patients starting conditioning, all donors should arrive in Beijing more than 2 weeks in advance and comply with home quarantine. Before donation, physicians should identify the presence of possible COVID-19 symptoms, history of travel to epidemic regions or close contact with persons with proven or suspected infection within the previous 30 days. Chest computed tomography (CT) and a test for SARS-CoV-2 are required in all donors. If either of these tests is positive, the potential donor should be rejected, or transplantation should be delayed.

For patients with indications for emergency transplantation, COVID-19 status should be immediately assessed from the patient's recent epidemiological history, respiratory infection history, clinical manifestations, and laboratory and radiographic testing, including temperature, SARS-CoV-2 testing, and chest CT scanning before permitting entry into inpatient clinics.

Key point

- We recommend preservation of transplant activity to the extent that the outbreak of COVID-19 allows.
- To minimize the risk of infection, preventive measures and strict screenings are of vital importance in each section of transplantation.
- Haploidentical donors are preferred over unrelated donors for reducing the uncertainty of COVID-19, and fresh PBSCs as graft source.
- Telemedicine is advocated in the regular follow-up after transplantation.

3.2 | Changes in special care of recipients after transplantation

Recipients with posttransplant comorbidities, such as active graft-versus-host disease (GvHD), infection and poor graft function, should be kept in the hospital. The following special care should be provided to recipients during hospitalization: (a) maintain hand hygiene; (b) separate in a ward for each patient to avoid cross-infection; (c) open windows without generating sudden changes in temperatures (recommended in non-epicenter); (d) wearing of a surgical mask at all times; (e) ensure a fixed caregiver to reduce the risk of cross-infection; and (f) refuse visitors as much as possible to transplant floors.

Patients may be discharged from the hospital in the absence of serious complications after transplantation. The following items should be included as prevention advice for home care: (a) wash hands frequently according to WHO recommendations, especially after blowing one's nose, coughing or sneezing, and after direct contact with sick people or their surroundings; (b) clean house surfaces regularly and ventilate the rooms with fresh air; (c) avoid crowded places or any contact with family and friends with COVID-19 symptoms/possible exposure; and (d) practice social distancing with all people to protect themselves.

Particularly, regular follow-up after transplantation is of vital importance to recipients. We advocate strategies to accelerate remote care and reduce unnecessary clinic visits. Essential posttransplantation laboratory testing (eg, CBC, CsA concentration, and CMV/EBV testing) should be performed in settings with minimal contact with staff or other patients, preferably home blood drawing if possible. Patients are advised to remain in contact with their physician-in-charge and report new symptoms or laboratory tests via telemedicine first. For patients who must be seen in the clinic, it is important to make an appointment online in advance. Consideration should be given to having patients wait in their cars or outside the facility prior to their appointment to promote social distancing because of the overcrowding of clinics and high risk of COVID-19. More importantly, recipients must remember to wear masks properly when going to the clinic.

3.3 | Preventive measures for caregivers and medical staff

Replacing caregivers for a patient certainly increases the mobility of the transplant ward and the risk of infection. As a result, each patient should receive a fixed caregiver during hospitalization. Similarly, the caregiver should be checked, including high-risk travel or contact history, respiratory symptoms, chest CT, as well as nucleic acid and antibodies of COVID-19, before entering transplant wards.

Another focus is to minimize cross-infection caused by medical staff as much as possible. In our centre, hospital staff were trained for preventive measures with sufficient quality. Daily temperature monitoring of all healthcare workers was mandatory to identify anyone who was unwell. Staff with respiratory symptoms or fever should stay at home. The wearing of surgical masks and disposable hats is required for staff in medical work in our centre. For healthcare providers involved in suspected COVID-19 cases, level 3 infection control precautions should be practised throughout the perioperative period. This practice minimizes the risk of cross-infection of patients and healthcare workers. (Table 1).

4 | TESTING, DIFFERENTIAL DIAGNOSIS, AND TREATMENT EXPERIENCE FOR COVID-19 IN TRANSPLANTATION

4.1 | Testing practices for COVID-19

The current gold standard as the diagnostic work-up of COVID-19 is real-time reverse transcription polymerase chain reaction (rRT-PCR) on respiratory tract specimens. According to the current diagnostic criteria of the China National Health Commission,¹⁴ both etiological and serological tests are conducive to confirm the diagnosis. In our practice, both PCR and specific COVID-19 antibodies (IgG and IgM) are measured for disease detection during screening.

TABLE 1 Suggested screening and preventive strategies in different settings

Settings	Suggested screening and preventive measures
Screening among patients before HSCT, donors, and caregivers	(i) Presence of possible COVID-19 symptoms; (ii) History of travel to epidemic regions or close contact with cases with proven or suspected infection; (iii) Chest CT and PCR assay and specific antibodies for SARS-CoV-2.
Prevention among patients in hospital after HSCT	(i) Maintain hand hygiene; (ii) Open windows in a timely manner (non-epicenter); (iii) Separate in a ward for each patient; (iv) Wear surgical mask at all times; (v) Ensure a fixed caregiver and prohibit visitors.
Prevention among patients out of hospital after HSCT	(i) Wash hands frequently according to WHO recommendations; (ii) Clean house regularly and ventilate rooms with fresh air; (iii) Avoid crowded places or any contact with family and friends with COVID-19 symptoms/possible exposure, and practice social distancing with all people; (iv) Telemedicine for regular follow-up, if necessary for a clinic visit, make an appointment in advance.

4.2 | Handling of candidates with COVID-19

In our centre, we had no cases of transplant candidates infected with COVID-19. As recommended by EBMT guidelines, if a patient with planned transplant is diagnosed with COVID-19, transplantation should be deferred until the patient is asymptomatic and has 2 repeated virus PCR negativity at least 1 week apart for patients with high-risk disease. In patients with low risk disease, a 3-month transplantation deferral is recommended.

4.3 | Differential diagnosis with COVID-19 in transplantation recipients

Recipients after transplantation are immunocompromised and prone to bacterial and various viral infections. Clinical and biochemical data of COVID-19 may be partially masked by coexisting infections. When patients have fever and lung shadows, infection with COVID-19 must be identified or excluded. According to the "New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Version 7)" issued by the China National Health Commission, initial laboratory tests include complete blood count, C-reactive protein (CRP), procalcitonin (PCT), transaminase, lactic dehydrogenase (LDH), creatase, and myohemoglobin levels.¹⁴ In our centre, a multiplex PCR respiratory pathogen panel is also applied for common differentials in addition to COVID-19, including parainfluenza virus (PIV), respiratory syncytial virus (RSV), human rhinovirus (HRV), mycoplasma pneumoniae (MP) etc History of travel or close contact and SARS-CoV-2 tests are irreplaceable for definite diagnoses of COVID-19.

Patients must be isolated in fever clinics before COVID-19 infection is excluded. At this time, transplant specialists in our centre go to the isolation area and give professional guidance to ensure standard treatment of complications posttransplantation. Once COVID-19 is excluded, patients are admitted to the transplant ward for further treatment.

4.4 | Treatment progression in transplant recipients with COVID-19

As for the treatment and management of patients with COVID-19, the Chinese New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Version 7) also provides detailed recommendations, including promising antivirals, anticytokine, or immunomodulatory agents, immunoglobulin therapy (COVID-19 convalescent plasma), traditional Chinese medicine, and the use of corticosteroids and supportive technologies (such as ECMO) in cases with ARDS.¹⁴

When considering treatment in transplant recipients, paying attention to drug-drug interactions and toxicity, particularly QTc prolongation, and close cardiac monitoring are recommended by the American Society for Transplantation and Cellular Therapy (ASTCT).¹⁵ However, there are no approved treatment options currently.

5 | SUMMARY

During the outbreak, we maintained 80% of the transplant status. None of the patients or staff in our centre have been diagnosed with COVID-19, which demonstrates the importance and effectiveness of our preventive measures. We recommend preservation of transplant activity to the extent that the outbreak of COVID-19 allows. Otherwise, numerous patients will miss the optimal opportunity of transplantation and have poor prognosis. In addition to preserving transplantation activity, ensuring the safety of transplantation is a top priority. As mentioned above, transplantation is a procedure involving many aspects, and maximum emphasis should be placed on radical preventive and screening measures for each section of transplantation.

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ETHICS STATEMENT

The comment was approved by the Institutional Review Board of Peking University People's Hospital.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

X.-J. H. designed the review; Z.-L. X. and X.-J. H. wrote the manuscript; and they gave final approval for the manuscript.

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