

# Guidance for Facing Dilemmas of Hematopoietic Stem Cell Transplant Clinicians in the Coronavirus Disease 2019 (COVID-19) Pandemic: An Iranian Consensus

<i>Seied Asadollah Mousavi</i>	Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
<i>Sorosh Rad</i>	Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
<i>Tahereh Rostami</i>	Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
<i>Mohammad Vaezi</i> <i>Hosein Kamranzadeh</i>	Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
<i>Davood Babakhani</i> <i>Sahar Tavakoli</i> <i>Maryam Barkhordar</i>	Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
<i>Tanaz Bahri</i>	Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
<i>Amirabbas Hedayatiasl</i> <i>Azadeh Kiumarsi</i>	Pediatric Hematologist and Oncologist

**Background:** COVID-19 has been declared as a public health emergency and a pandemic by World Health Organization. Among high-risk patients infected by the virus, hematopoietic stem cell transplant (HSCT) recipients are vulnerable to severe presentation of this infection. Thus, the necessity for precise strategies in dealing with HSCT recipients in this pandemic seems inevitable.

**Methods:** We discussed the dilemmas brought up by the emergence of COVID-19 in the management of HSCT recipients, through a virtual panel of experts, considering the latest available records about COVID-19. About each enquiry, we have provided the consensus of the clinicians and paraclinicians in our center.

**Recommendations:** We agreed to choose more precautionary strategies and less optimal policies. The amendments aim to reduce the risk of exposure to COVID-19 in our patients and also in our health care provider team.

---

## Introduction

Coronavirus Disease 2019 (COVID-19) has been classified as a pandemic by World Health Organization since March 2020 [1]. The number of involved cases is increasing rapidly around the

world and its burden on health care system is progressively growing. Most countries have restricted their gatherings, travels, and other aspects of life. These restrictions would surely impact the transplant activities in many centers. Although all people are susceptible to this infection, hematopoietic stem cell transplant (HSCT) recipients are at increased risk and dissimilar to other respiratory viruses, little is known about the clinical significance of human coronavirus infection in this population.

Therefore, in this paper, we have provided the recommendations from hematology-oncology and stem cell transplant research center (HORCSCT) experts on managing HSCT recipients and donors in COVID-19 pandemic. It is imperative to note that data about this disease and its impact on our patients is evolving and so our strategy is to repeatedly update the guidance as soon as new information becomes accessible.

## **Epidemiology and clinical features**

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARSCoV-2), which is a novel single-stranded enveloped RNA virus. Respiratory droplets are the most important route of transmission but it can also be aerosolized or detected in the stool. As noted by Food and Drug Administration (FDA), transfusion-transmitted coronaviruses has not been reported till now [2]. The virus incubation time is estimated to be 2-14 days [3]. Early reports suggest that the majority of patients have mild symptoms with the most common being fever and dry cough [4]. Moreover, symptoms related to the digestive systems, such as nausea and diarrhea, and ophthalmic symptoms are also part of the clinical manifestations [5]. Nevertheless, the asymptomatic patients are important sources of transmission during the incubation period or in early stages of infection [6]. Imaging manifestations include multiple small patchy shadows and interstitial changes at an early stage, which gradually progresses to multiple ground-glass and infiltration opacities in both lungs during the progressive stage [7]. Patients with COVID-19 are prone to have a decrease in lymphocyte counts, and levels of inflammatory markers, such as C-reactive protein (CRP), may be elevated in some patients to a varying degree [8]. Mortality seems to be age dependent, with the highest proportions in older patients. Even though co-morbidities have been reported in most case series, documented data about transplant patients is limited and a sketch of the disease in HSCT recipients is not yet available. The main diagnostic test is RT-PCR of nasopharyngeal, oropharyngeal and lower respiratory tract samples. It should be noted that following infection, median viral shedding of 20 days is anticipated which might be more prolonged in immunosuppressed patients and may last up to 4 weeks [9]. For treatment, antiviral drugs such as lopinavir-ritonavir and remdesivir and anti-cytokine therapies such as tocilizumab are under exploration in different clinical trials [10].

## **Methods**

The existing guidelines about the management of HSCT patients in COVID-19 pandemic were discussed among HORCSCT experts through a virtual panel [11]. Considering the available updates on COVID-19, we debated on the proposed dilemmas and the frequently asked questions by patients and health care professionals and then we documented the consensus of all members in the related disciplines.

## **Recommendations**

Based on the experiences with other infectious disease, the available health care facilities in our country, and the existing data in the literature, these recommendations are proposed for the time being and they would be updated as soon as new information about COVID-19 epidemiology and clinical outcomes would become accessible.

## **In HSCT candidates**

- In patients not known to have COVID-19 (asymptomatic (The significant considered symptoms are fever, cough, shortness of breath) AND no history of close contact with a diagnosed case of COVID-19)- Recommend patients for home isolation 14 days before hospital admission.- Check for CBC, Diff, CRP and COVID-19 test by RT-PCR before admission.- A negative result of COVID-19 test (by RT-PCR), 48 hours before the initiation of conditioning regimen is demanded. • Patients known or suspected to have COVID-19 (symptomatic OR history of close contact with a diagnosed case of COVID-19)

- Check for CBC, Diff, CRP, COVID-19 test by RT- PCR and chest CT scan before admission.

- For patients with a positive RT-PCR test for COVID-19 or chest CT scan suspicious of COVID-19, who are considered high risk for disease progression (i.e. acute leukemia, high-grade lymphomas), HSCT should be deferred until symptoms are resolved AND two separate negative RT-PCR tests, at least 1 week apart, are obtained.

- For patients with a positive RT-PCR test for COVID-19 whose underlying disease is considered low risk, HSCT should be deferred for at least 3 months.

- In patients who have a history of close contact with a known case of COVID-19, but their RT-PCR test for COVID-19 is negative and their chest CT scan is normal, conditioning regimen should be deferred until 14 days after the mentioned contact AND one negative RT-PCR test should be obtained before the initiation of conditioning regimen.

- Defer following autologous HSCTs until the risks associated with the COVID 19 pandemic have passed: non-urgent indications (i.e. Multiple Myeloma in first complete remission (As some novel agents like Ibrutinib or Daratumumab aren't easily available for multiple myeloma patients, we can only defer auto-HSCT for patients in their first complete remission), low-grade lymphoproliferative diseases, and consolidative transplants for solid tumors such as germ cell tumors) and non-malignant indications.

- Defer following allogeneic HSCTs until the risks associated with the COVID 19 pandemic have passed: HSCTs from international unrelated donor and HSCTs for non-malignant disorders (i.e. Thalassemia, etc.)

## **In stem cell donors**

Few is known about the risk of COVID-19 transmission from donor to recipient. Attention to donor epidemiological risk factors may help to weaken the risk of donor transmitted infection [12].

- In donors not known to have COVID-19 (asymptomatic AND no history of close contact with a diagnosed case of COVID-19)

- Recommend donors to sustain good hygiene and avoid crowded residences for at least 28 days before donation.

- Test for COVID-19 by RT-PCR one day before the initiation of conditioning regimen.

- In donors suspected to have COVID-19 (symptomatic OR history of close contact with a diagnosed case of COVID-19)

- Check for COVID-19 test by RT-PCR and chest CT scan.
- In donors with a history of close contact with a diagnosed case of COVID-19, if the RT-PCR test for COVID-19 is negative AND the chest CT scan is normal, the donor would be considered eligible for donation if 14 days has passed from the mentioned last contact AND one negative RT-PCR test obtained before starting conditioning regimen.
- If the RT-PCR test for COVID-19 is positive OR the chest CT scan is suspicious of COVID-19, the donor would be considered ineligible to donate for at least 3 months after the complete resolution of symptoms.
- If HSCT is urgent and there are no alternative suitable donors available, re-consider the donor's eligibility; if at least 28 days has passed from complete resolution of symptoms AND there is no history of severe respiratory disease AND one negative RT-PCR test could be obtained before starting conditioning regimen, the donor would be considered eligible for donation.
- As harvesting stem cells from bone marrow requires anaesthesia and referring the donor to the general operation room, in which the donor may be exposed to COVID-19, we prefer to choose peripheral blood as the source of stem cells, for the time being.

## **Recommendations for HSCT recipient's caregiver**

- The patient should not have a caregiver if possible.
- The caregiver's COVID-19 RT-PCR test should be negative before entering HSCT ward.
- Caregivers with COVID-19 symptoms are ineligible and should be referred to national guideline for diagnosis and management of COVID-19.
- Caregivers who have a history of close contact with a diagnosed COVID-19 case, should avoid contacting the patient for at least 14 days after the mentioned contact and obtain a negative COVID-19 RT-PCR test before entering the HSCT unit.

## **Recommendations for HSCT unit**

- SARS-CoV-2 is sensitive to ultraviolet rays and heat. The virus can be effectively inactivated under conditions of 56 °C for 30 min, using ether, 75% alcohol, chlorine-containing disinfectant, and chloroform [13]. Disinfection of HSCT wards should be performed with alcohol containing disinfectants.
- People's commute in HSCT unit should be restricted as much as possible and non-essential staff & student contact with inpatients should be reduced.
- Face-to-face educational assemblies should be postponed and education should be provided via teleconferencing or other electronic layouts [14].
- The HSCT unit's workforce including administrators, ward staff, and clinicians should be re-educated about hand hygiene practices, policies for respiratory virus isolation and the major associated symptoms of COVID-19.
- RT-PCR for COVID-19 is planned to be offered as a screening tool, every two weeks in HSCT

units' working staff.

- If employees of HSCT units are symptomatic or have a history of close contact with a diagnosed case of COVID-19, they should leave the unit immediately and should be referred to national guideline of diagnosis and management of COVID-19.

### **Recommendations for recipients in post-transplant phase:**

- Patients after being discharged from transplant unit should limit their contacts with potentially infected people.
- Patients should adhere to national prevention guidelines recommendations such as hand hygiene, home isolation and social distancing.
- Patients may use cyber network or telephone contact with healthcare providers to manage their non-emergent problems in order to reduce the frequency of travels to the hospital.
- Prophylaxis after HSCT with hydroxychloroquine sulfate 400 mg as single dose (Pediatric dose: 6.5 mg/kg, not to exceed 400 mg) every 3 weeks since engraftment until the COVID-19 pandemic has lapsed, is recommended.

### **Diagnosis and treatment of COVID-19 in HSCT patients**

- For patients with upper or lower respiratory symptoms and for patients who have a history of close contact with a person diagnosed with COVID-19, RT-PCR test for COVID-19 and chest CT scan should be considered.
- Routine bronchoalveolar lavage (BAL) is not recommended if patient has a positive RT-PCR test for COVID-19 unless a co-infection is suspected.
- If RT-PCR test for COVID-19 is positive or chest CT scan is suspicious of COVID-19, patient should be managed and treated according to national COVID-19 guideline.
- Optimal management strategies have not been determined. Supportive care is the mainstay of therapy.
- For prophylaxy and treatment of graft versus host disease, immunosuppressive therapy should be continued. Drug-drug interactions of anti-viral drugs with calcineurin inhibitors should be kept in mind.

Finally, the emergence of COVID-19 is a global crisis that the transplant community has been forced to face. We should learn from our experiences and implement the best possible strategies in order to protect our transplant recipients and also the healthcare providers.

## **Acknowledgments**

### **Disclosure**

The authors have no conflicts of interest in this manuscript.

## References

## References

1. Branswell H, Joseph A. WHO declares the coronavirus outbreak a pandemic 2020 Available from: <https://www.statnews.com/2020/03/11/whodeclares-the-coronavirus-outbreak-a-pandemic>.
2. Important information for blood establishments regarding the novel coronavirus outbreak. Available from: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-information-blood-establishments-regarding-novel-coronavirus-outbreak>. Accessed February 15, 2020.
3. Chen Nanshan, Zhou Min, Dong Xuan, Qu Jieming, Gong Fengyun, Han Yang, Qiu Yang, Wang Jingli, Liu Ying, Wei Yuan, Xia Jia'an, Yu Ting, Zhang Xinxin, Zhang Li. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020; 395(10223)[DOI](#)
4. Clerkin Kevin J., Fried Justin A., Raikhelkar Jayant, Sayer Gabriel, Griffin Jan M., Masoumi Amirali, Jain Sneha S., Burkhoff Daniel, Kumaraiah Deepa, Rabbani LeRoy, Schwartz Allan, Uriel Nir. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. *Circulation*. 2020. [DOI](#)
5. Zhang Zhan, Li Xiaochen, Zhang Wei, Shi Zheng-Li, Zheng Zhishui, Wang Tao. Clinical Features and Treatment of 2019-nCoV Pneumonia Patients in Wuhan: Report of A Couple Cases. *Virologica Sinica*. 2020. [DOI](#)
6. Ju Chun-Rong, Lian Qiao-Yan, Zhang Jian-Heng, Qiu Tao, Cai Zhi-Tao, Jiang Wen-Yang, Zhang Jing, Cheng Qin, Chen Gang, Li Ning, Wang Chun-Yan, He Jian-Xing. Recommended prophylactic and management strategies for severe acute respiratory syndrome coronavirus 2 infection in transplant recipients. *Chronic Diseases and Translational Medicine*. 2020. [DOI](#)
7. Fang Yicheng, Zhang Huangqi, Xu Yunyu, Xie Jicheng, Pang Peipei, Ji Wenbin. CT Manifestations of Two Cases of 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology*. 2020; 295(1)[DOI](#)
8. Bernheim Adam, Mei Xueyan, Huang Mingqian, Yang Yang, Fayad Zahi A., Zhang Ning, Diao Kaiyue, Lin Bin, Zhu Xiqi, Li Kunwei, Li Shaolin, Shan Hong, Jacobi Adam, Chung Michael. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology*. 2020. [DOI](#)
9. Kotton Camille N., Kumar Deepali, Caliendo Angela M., Huprikar Shirish, Chou Sunwen, Danziger-Isakov Lara, Humar Atul. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. *Transplantation*. 2018; 102(6)[DOI](#)
10. Eichenberger Emily M., Soave Rosemary, Zappetti Dana, Small Catherine B., Shore Tsiporah, van Besien Koen, Douglass Claire, Westblade Lars F., Satlin Michael J.. Incidence, significance, and persistence of human coronavirus infection in hematopoietic stem cell transplant recipients. *Bone Marrow Transplantation*. 2018; 54(7)[DOI](#)
11. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-managementpatients.html>.
12. COVID-19 rapid guideline: haematopoietic stem cell transplantation NICE guideline [NG164] Published date: 01 April 2020. Available from: <https://www.nice.org.uk/guidance/ng164/EBMT;2020> [updated 03/30/2020]. Available from: <https://www.ebmt.org/sites/default/files/2020-03/EBMT%20COVID19%20guidelines%20v.5.1%20%282020-03-30%29.pdf>.
13. Interim guidelines for covid-19 management in hematopoietic cell transplant and cellular therapy patients Version 1.1 March 9, 2020. Available from: [https://higherlogicdownload.s3.amazonaws.com/ASBMT/a1e2ac9a-36d2-4e23-945c-45118b667268/UploadedImages/COVID19\\_Interim\\_Patient\\_Guidelines\\_3\\_9\\_20\\_V2.pdf](https://higherlogicdownload.s3.amazonaws.com/ASBMT/a1e2ac9a-36d2-4e23-945c-45118b667268/UploadedImages/COVID19_Interim_Patient_Guidelines_3_9_20_V2.pdf).
14. Michaels Marian G., La Hoz Ricardo M., Danziger-Isakov Lara, Blumberg Emily A., Kumar



Deepali, Green Michael, Pruett Timothy L., Wolfe Cameron R.. Coronavirus disease 2019: Implications of emerging infections for transplantation. *American Journal of Transplantation*. 2020. [DOI](#)