**INTRODUCTION**

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, has caused a global pandemic with 2,503,472 cases and 171,810 deaths as of 21 April 2020. In the United States alone, there have been 792,958 cases and 42,531 deaths. COVID-19 was first reported in Wuhan, Hubei, China in December 2019. Since then, it has spread to over 200 countries worldwide. Prevention methods to help curb the spread of the virus such as hand washing, avoiding close contact with sick individuals, social distancing, wearing face masks, and cleaning and disinfecting frequently, have been able to “flatten the curve” somewhat but has not completely stopped the spread of the virus. SARS-CoV-2 virus is transmitted from human-to-human after a 1 to 14 day incubation period via respiratory droplets and causes flu-like symptoms such as fever, coughing, breathing difficulties, fatigue and myalgias.

Columbia University Irving Medical Center/NewYork-Presbyterian Hospital (CUIMC/NYPH) has very active blood and marrow transplant programs (BMT) for both pediatric and adult patients. About 100 transplants are performed each year for patients with benign and malignant hematological diseases. In 2019, the pediatric BMT program transplanted 13 autologous patients and 20 allogeneic patients. They also performed 2 CD34+ cell boosts without conditioning, 3 chimeric antigen receptor (CAR)-T cell infusions and 9 cytotoxic T cell infusions. The adult BMT program performed 44 autologous transplants and 23 allogeneic transplants, 17 CAR-T cell infusions, and 3 donor lymphocyte infusions/CD34+ cell boosts.

The Cellular Therapy Laboratory (CTL) processes approximately 160 Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) a year from bone marrow harvests, peripheral blood stem cell (PBSC) collections via apheresis, and cord blood products. Autologous products are routinely cryopreserved while most allogeneic products are infused fresh into recipients. Since New York is at the epicenter of the COVID-19 pandemic with 132,467 cases, 34,729 hospitalized and 9,101 deaths to date (20 April 2020), it was clear that we had to make changes to our clinical, collection and processing operations in order to protect the health and safety of our donors, recipients, and staff. In this article, we discuss the process changes we made to the various steps leading up to BMT in order to be able to adapt to the evolving cellular therapy landscape during the COVID-19 pandemic.

**DONOR AND RECIPIENT TESTING**

Pediatric BMT donors are evaluated 48 hours prior to stem cell collection. The transplant nurse coordinator
assesses the donors by conducting a review of systems to evaluate for COVID-19 symptoms and takes a history of potential exposures. A viral respiratory swab is also obtained to test for the presence of the SARS-CoV-2 virus. If the donor tests negative, the donor proceeds with the donation. If the donor tests positive for the SARS-CoV-2 virus, the collection is delayed and re-testing is performed between 7-14 days, depending on the urgency of treatment, after the initial testing and when they have been symptom free for 3 days. Adult BMT donors are tested for the SARS-CoV-2 virus prior to mobilization for PBSC collection. If a donor tests positive, they are deferred for 28 days and retested 24 hours prior to the start of mobilization.

Pediatric BMT recipients are evaluated by a BMT provider 48 hours prior to the start of conditioning. Similar to donors, the recipients are assessed for the presence of COVID-19 symptoms and history of potential exposures. A viral respiratory swab is obtained to test for the presence of the SARS-CoV-2 virus. The BMT would proceed if the test result is negative. If the recipient is found to be positive for the SARS-CoV-2 virus, the transplant is delayed and the recipient is re-tested in 7-14 days, depending on the urgency of the transplant, after the initial test and when the recipient has been free of symptoms for 3 days. If re-testing is negative, care is resumed. If re-testing is positive, recipients are reassessed/re-tested and the urgency of their treatment is re-assessed. Adult recipients are tested for the SARS-CoV-2 virus 24 hours prior to admission.

Pediatric BMT recipient caregivers are also tested along with the recipient prior to admission. If the caregiver is symptomatic, they are not allowed to accompany the patient and an asymptomatic caregiver is substituted, if possible. Symptomatic caregivers are sent home or referred to the emergency department if necessary. Caregivers may be re-tested based on history.

3 | DONOR SUITABILITY AND ELIGIBILITY DETERMINATIONS

Donor suitability and eligibility determinations are performed prior to donation according to regulatory requirements (eg, Food and Drug Administration, New York State Department of Health) and accreditation (eg, Foundation for the Accreditation of Cellular Therapy) standards. Donor suitability is still performed in-person due to the need to do a physical exam and draw blood for laboratory testing including infectious disease marker testing. Donor eligibility is determined via telemedicine after the completed donor eligibility questionnaire is provided to the transfusion medicine physician. Since AABB guidelines do not recommend screening for SARS-CoV-2 in blood products because there is no evidence for transfusion transmission nor is there a precedent suggesting a risk for transfusion transmission, no additional screening or testing is performed at the time of donor eligibility determination. Donor screening and testing is performed more proximal to the actual collection date by the BMT teams as outlined above.

4 | DONOR PBSC COLLECTION

Donors are scheduled for PBSC collection procedures only after they have passed screening by the BMT teams. Outpatients presenting for PBSC collection in the apheresis unit are screened for the presence of COVID-19 symptoms; namely, fever, cough, shortness of breath, and/or sore throat. If the patient is asymptomatic, the registration process continues. If the patient endorses any symptoms associated with COVID-19, the patient and anyone accompanying the patient is asked to don a surgical mask and perform hand hygiene. The patient and anyone accompanying the patient is relocated to a private exam room. If one is not available, the patient is separated from other patients by at least 6 feet. Clinicians entering the room don the proper PPE (ie, face mask with eye protection, gown and gloves) and obtain additional information from the patient: signs and symptoms and dates of onset, travel history (dates, locations), history of exposure to ill persons who are confirmed or suspected to have COVID-19. Donors suspected of having COVID-19 are deferred from donation and referred to their BMT physician for further management.

Providers performing the PBSC collection or bone marrow harvest follow universal precautions and don the appropriate PPE according to institution policies for proper personal protective equipment (PPE) during the COVID-19 pandemic which include N95 masks, face shields, gown, and gloves.

The number of collections from 1 March 2020 to 15 April 2020 is similar to the number of collections for the same period in 2018 and is increased compared to 2019 (Figure 1). By instituting precautionary measures, we were able to maintain the same level of operation in the Apheresis Unit while protecting the safety and well-being of our patients and healthcare providers.

5 | PRODUCT PROCESSING

Prior to the COVID-19 pandemic, only autologous products were cryopreserved on a routine basis. Most allogeneic products were infused fresh and not cryopreserved.
With the advent of COVID-19, both autologous and allogeneic products (from related and unrelated donors) are cryopreserved. This is in line with the National Marrow Donor Program’s strong recommendation initially (9 March 2020) and a requirement as of 30 March 2020 that all transplant centers plan to receive and cryopreserve unrelated donor product prior to initiation of patient conditioning. This ensures that recipients who complete myeloablative conditioning are able to receive donor cells on day 0.

The number of products that were processed remained steady during the period 1 March 2020 to 15 April 2020 when compared to the same period in 2018 and is double that of 2019 (Figure 1). In anticipation of potential staff attrition due to the COVID-19 pandemic, our standard operating procedures (SOPs) for processing and cryopreservation were re-evaluated and revised to increase efficiency. Prior to the pandemic, after plasma reduction, a sample of the post-processing product was sent to the automated lab for a complete blood count to determine the total nucleated cell (TNC) count. With the advent of COVID-19, the TNC count post plasma reduction is assumed to be 95% of the pre-processed sample based on the mean TNC recovery data compiled from 26 products. Prior to COVID-19, the cryoprotectant solution is prepared fresh each day. During the COVID-19 pandemic, the cryoprotectant solution is prepared in batches with an expiration of 29 days in order to save time and financial resources. This expiration was arbitrarily chosen based on the practices of other peer institutions and was validated for sterility, appearance and post-thaw TNC viability. Because a larger number of units are being cryopreserved compared to the similar period in previous years (Figure 1), the requirement for liquid nitrogen freezer space was anticipated to increase. Heroic efforts were made to identify and discard deceased donor products to create more space in the liquid nitrogen freezers. In addition, off-site storage solutions are being explored to increase freezer capacity.

All CTL SOPs were reviewed to maximize operational efficiency and reduce redundancy. Electronic forms such as those for event reporting, validation plans, validation reports and process change control were developed to allow remote review and approvals by the medical director. Supply logs and the master supply lists were converted from paper to electronic format. New vendors were qualified to have an alternate source for supplies that are backordered. Staffing contingency plans were developed to minimize workflow disruptions in the event that any staff member falls ill. All lab meetings are conducted via teleconferencing. Non-essential projects were put on hold and focus has been placed on maximizing the lab’s capacity for processing work during the pandemic. Work in the current good manufacturing practices laboratory was put on hold in order to conserve PPE. All staff members don the appropriate PPE while processing according to the usual practice which includes gloves, lab coat, and face shield (biohazard only). A face mask is now also worn at all times as part of the COVID-19 safety measure. In addition, lab coats are changed weekly or when soiled as opposed to changing daily prior to the pandemic.

6 | TRANSPLANTATION

Both pediatric and adult BMT programs postponed all non-malignant elective transplants such as those for patients with hemoglobinopathies (eg, sickle cell disease and thalassemia). In addition, the adult BMT program also delayed all myeloma and plasma cell dyscrasia transplants. Patients were being evaluated on a case by case basis to determine the need for BMT during the COVID-19 pandemic based on their disease status and acuity. Despite this, the pediatric and adult BMT programs remained active. With the institution of safety measures, patients who were determined to need a transplant emergently were able to receive one. As such, there had been no decline in the number of BMT performed from 1 March 2020 to 15 April 2020 compared to the same period in previous years (Figure 1).

We continued to provide CAR T cell therapy to patients during the COVID-19 pandemic. We performed PBSC collections for and infusions of Yescarta (Kite...
Pharma, Los Angeles, CA, USA) and Kymriah (Novartis, Basel, Switzerland) according to our usual protocol. Clinic visits were performed via telemedicine through EPIC for patients who did not require to be physically seen by a provider. Required blood tests were performed at Quest or Labcorp facilities when necessary. Recipients started conditioning regimens only after the cryopreserved product was confirmed to be in the custody of the CTL. This avoided the situation where a recipient completed myeloablative conditioning and the donor was acutely unable to donate due to illness or placed in quarantine.

7 | CLINICAL TRIALS

When the pandemic started, CUIMC/NYPH ramped down clinical trial activities. Only essential research or essential functions to maintain critical research resources were allowed. The Institutional Review Board (IRB) had contacted each investigator via individual, automated emails asking the Principal Investigator (PI) to answer a series of questions to assess the risk/benefit ratio for their trial to determine if the research should continue or temporarily pause. The Herbert Irving Comprehensive Cancer Care Center leadership determined during the early days of the pandemic that all interventional/therapeutic clinical trials for oncologic indications should continue because the clinical trials offered a benefit to the patients that was greater than the risk. As the pandemic raged on in New York City; however, all enrollment on therapeutic cancer trials were placed on hold.

8 | DISCUSSION

The COVID-19 pandemic has changed the cellular therapy landscape at CUIMC/NYPH. Operational changes had to be made across the clinical, collection and processing programs in order to minimize the risk to BMT donors and recipients. As the COVID-19 pandemic continues to evolve in New York state, we need to be prepared to further adapt our policies and procedures to minimize risk and maximize benefit for our patients.

The data presented in Figure 1 only includes statistics for the period starting 1 March and ending 15 April for 2018, 2019 and 2020. The activities carried out from week to week and month to month in any given year varies. However, our statistics have remained relatively constant in the last couple of years. In 2018, we collected 88 patients, processed 157 products and infused 115 products. In 2019, we collected 89 patients, processed 189 products and infused 105 products. The total number of products we processed in 2019 was actually greater than in 2018 despite the lower numbers in the March/April time frame. The decrease in activity by the BMT programs (ie, only preforming urgent transplants) when the pandemic started also contributed to the lack of a significant increase in the amount of products processed in 2020 compared to previous years. As the pandemic slows and clinical operations ramp up, we expect to see an increase in the numbers again.

To date, there have been no reports of transfusion-transmitted COVID-19 even though SARS-CoV-2 has been found in routine blood donations by researchers in China and South Korea.\(^6\)\(^7\) Chang et al reported detecting the SARS-CoV-2 RNA in platelet and plasma products collected at the Wuhan Blood Center using the real-time reverse transcription PCR (RT-PCR) for SARS-CoV-2 RNA by using MultiScreen Pro RT-PCR assay (SYM-BIO LifeScience, PerkinElmer, Waltham, MA, USA).\(^7\) Follow-up interview with these donors revealed that some of them developed fever after donation which resolved over several days. In South Korea, Kwon et al detected SARS-CoV-2 RNA in whole blood donations and source plasma donations. Products that had not been transfused were recalled. Patients who were transfused with SARS-CoV-2 contaminated platelet and red blood cell products did not develop symptoms 19-29 days after receiving the labile blood products or tested positive for SARS-CoV-2 RNA.\(^6\) Precautionary measures should continuously be re-evaluated as our understanding of the virus increases and followed even though no transfusion-transmission of SARS-CoV-2 virus in stem cell products has been reported so far.

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CONFLICT OF INTERESTS

The authors declare no potential conflict of interest.

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