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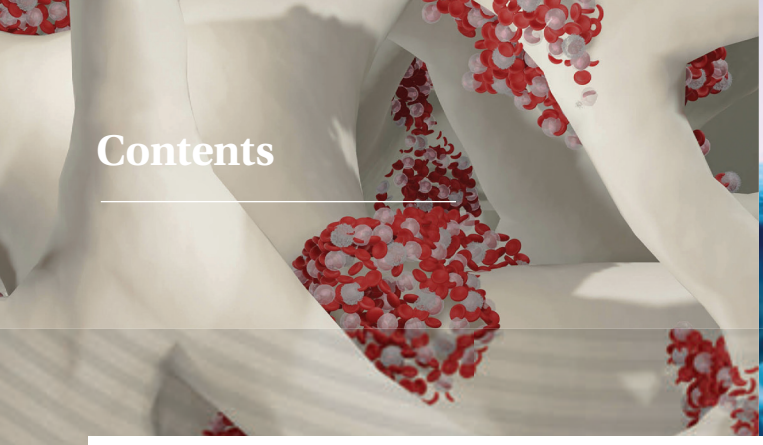
Advances in **Blood Products and Biotherapies**



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RECONSIDERING CRYOPRESERVATION FOR HPCs

How the COVID-19 pandemic impacted the delivery of stem cell transplantation

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The COVID-19 pandemic significantly impacted all facets of the blood and biotherapies field, causing widespread disruption to the supply and demand for blood and blood stem cell products. Travel bans, flight delays and border closures amid the lockdown posed logistical challenges for fresh donor products and jeopardized the delivery of allogeneic hematopoietic cell transplantation (HCT).

Growing patient and donor safety concerns and logistical hurdles spurred transplant centers to modify their procedures; many switched to the cryopreservation of allogeneic hematopoietic progenitor cell (HPC) grafts from related and unrelated donors to ensure patients had a viable (optimized) graft available on the day of planned HCT.[1] As a result, the use of cryopreservation for HPCs exploded as COVID-19 spread; only 7.4% of transplant centers were routinely cryopreserving HPC products pre-pandemic, and this percentage increased to 90% during the pandemic period.[2]

Once considered a last resort, cryopreservation offered patients a reliable treatment option when fresh grafts were less readily available or not possible, noted Laura Staller, MHA, MLS(ASCP)CM, manager of cryopreservation service at the National Marrow Donor Program (NMDP). NMDP's cryopreservation service allows the donor's collection to proceed before a patient's transplant. The donor's cells are cryopreserved and stored at one of its four partner facilities until the product is requested for shipment. If the patient's health status changes and they are unable to proceed to transplant, the service offers flexibility in scheduling collection, allowing for a delay that meets the recipient's needs.[3]

"Donor availability hurdles and/or patient-related postponements can be overcome through cryopreservation allowing for more flexibility in donation date and apheresis or collection center scheduling," Staller said. She noted that NMDP mandated the cryopreservation of nearly all hematopoietic cell grafts from volunteer unrelated donors in March 2020, with peak levels reaching 97% of products in April 2020.

"People have become more comfortable with cryopreservation," Staller added. "The indications for cryopreservation have expanded in terms of what is acceptable for use today. There is a wider variability of use cases as compared to pre-pandemic."

Navigating Hurdles and Risks

Melissa Marlowe, vice president of clinical services at Vitalant's Specialty Laboratories & Therapeutics Group Human Leukocyte Antigen (HLA), Cellular Therapy and Clinical Support Services, shared how the increased demand for cryopreservation during the pandemic drastically impacted her team's workflow and presented challenges to providing HPCs for patient transplants on a larger scale.

"We went from cryopreserving a few products per week for the NMDP—the majority of products were fresh infusions for local transplant programs—to handling multiple requests for cryopreservation each week and managing the logistics to ship products internationally, mainly to Australia," Marlowe said. Within two months, her center's volume went from 70% fresh products and 30% cryopreserved products to the reverse. "The additional complications with logistics during the first two years of the pandemic made the process extremely challenging," she said.

Common risks associated with cryopreservation include unexpected loss of viability due to donor graft response; lack of consensus on a post-thaw viability method for ancillary samples to evaluate products prior to thaw and infusion; cracked or broken bags leading to smaller cell doses than originally anticipated/collected; and real-time tracking of shipments. Depending on the reason for cryopreservation, there is also a risk that a cryopreserved donor product will not be used for transplant. In such instances where a donor product goes unused, if a donor product is cryopreserved through the NMDP cryopreservation service and the donor consents, the product can be listed for other searching patients in NMDP systems

"Transportation with validated shippers and pack out configurations provides reassurance of product integrity during shipping," Staller explained. "There's always a risk with a product that is going through additional steps for cryopreservation, though often, patient and donor considerations leading to cryopreservation supersede this consideration. Although validated laboratory methods minimize processing variation while maximizing post-thaw viability, the potential for some loss of cellular viability due to the cryopreservation and thaw process should be considered when determining the total cells to collect from the donor."

Another drawback of cryopreservation is the added costs to the procedure, which are dependent on

the donor supplier.[4] However, most transplant centers consider cryopreservation to be a necessary step to getting a patient to transplant, so the negligible costs rarely influence the decision, Staller pointed out.

"For most people considering cryopreservation, the financial component isn't such that it would prohibit them from proceeding," Staller said.

A recent study analyzed 1,543 recipients of cryopreserved allografts receiving HCT at U.S. centers during the first six months of the pandemic and compared them with 2,499 recipients of fresh allografts during a six-month period in 2019.[1] The results showed that although there was no significant impact of cryopreservation on the overall survival within one year after HCT, relapse and graft failure risks were higher and disease-free survival was lower relative to fresh product HCTs. The authors reported that cryopreservation poses no risk of major clinical compromise in outcomes when necessary to safeguard the provision of donor allografts. [1] However, the study's findings reveal that cryopreserved grafts are a safe and effective option when fresh grafts are not feasible.[5]

"Fresh products are always preferred at our institution like most places," said Diane Kadidlo, facility director for molecular and cellular therapeutics (MCT) at the University of Minnesota and technical supervisor of the M Health Fairview University of Minnesota Medical Center Cell Therapy Laboratory. Her AABB-accredited facility began its partnership with NMDP in 2020 to offer cryopreservation services to transplant centers through the NMDP cryopreservation service.

"We weren't freezing many allogenic peripheral stem cells before the pandemic. Cryopreservation helped to overcome logistical issues during a critical time, and I'm glad it was an option," Kadidlo said.

Collaborative Efforts

Collaborations have been key to the successful navigation of transplantation during the pandemic, providing additional cellular therapy laboratory capacity to centers who do not routinely cryopreserve their products. To that end, NMDP has provided cryopreservation services for more than 500 donor products through collaborations formed with its partner laboratories since 2020.

"We have a couple of transplant centers that use us exclusively for cryopreservation because they do not have the infrastructure to do it," Staller said. "Without the contracted laboratories of NMDP, transplant centers had few options for cryopreservation, with a patchwork of contracting and agreements tying up valuable resources. By providing a centralized cryopreservation service, NMDP has been able to add process uniformity and product consistency to the cryopreservation experience through our partner laboratories."

Although collaboration has contributed to successful outcomes, Staller highlighted ongoing considerations associated with a network of laboratories and vendors, including comprehensive process standardization; management of variables, including testing methods; and adoption of testing not routinely performed at sites.

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"The obstacles that present themselves regarding the art of processing are hard to account for," stated Ericka Narr, NMDP's senior manager of customer-ready products. "Processing will be different at each lab, even if they're using a similar instrument. Having specific, defined cryopreservation service laboratory partners helps streamline processes, however, 'apples to apples' is just not something that's easy to accomplish, or even feasible in many ways."

For Marlowe, successful outcomes in bio cell therapy service boil down to communication and collaboration. Understanding the needs for an individual patient's case is critical, she emphasized.

"We have our general process, but there is customization based on the needs of each clinical program and their transplant needs," Marlowe said, noting that the Vitalant Cell Therapy Lab, an NMDP partner and AABB-accredited facility, handles the processing, cryopreservation and storage for 11 different HSC and immune effector cell (IEC) transplant programs across five different states and for 14 commercial and clinical development products. "From a simplistic piece, we use a group e-mail for all communications including everyone from the medical director to the lab assistant, so there's not a gap in communication. Having everyone on the same page is critical."

Kadidlo shared the same sentiment and added that collaborating with NMDP and other organizations to provide cryopreservation services is a win-win for

patients and donors. "We are extremely proud that we can provide this service to those who needed centers to handle cryopreservation for them, especially during the pandemic. We feel fortunate to be a part of this collaborative effort," Kadidlo said.

Marlowe mentioned her hopes to see more collaborative efforts that support cryopreservation and expand access to patient care. "We've reached out to programs that want to do collections for these types of products; they are looking for support for cryopreservation, but they don't have local resources," Marlowe said. "We have a lot of expertise in different areas, but how do we work together within the field and AABB to fill those gaps and expand our networks to help them obtain the resources they need?"

A New Normal

Cryopreservation provided lifesaving opportunities at the time of patient need during the pandemic; however, research shows the demand for cryopreserved HPC products has dwindled in the post-pandemic era.[1] According to NMDP, the average rate of cryopreservation has leveled off at 23% for the past seven months, suggesting the seasonality of cryopreservation may not have as large an impact in 2024 as it did for the cold, flu and COVID-19 seasons of 2020-2023.

"The current rate is still higher than pre-pandemic level, and a contributing factor to today's volume is related to the manufacturing of cell therapy products," Marlowe said. She believes the increased volume in cell therapy — with multiple processing steps where geography and time are the enemy — is driving increased cryopreservation requests. "We are excited about this area of growth. Cryopreservation is opening new opportunities to expand patient access into places that might not have been previously available."

The potential benefits associated with the cryopreservation of HPC products extend beyond the pandemic. Both Staller and Narr recalled moments when cryopreservation helped to manage donors' cells and deliver a quality product for a patient transplant during natural disasters, such as the 2023 Texas ice storm and Hurricane Idalia in Florida. Staller noted that hurricanes, ice storms and snowstorms have all driven products into their sites due to the logistical coordination needed to overcome the uncertainties of these situations. With cryopreservation, the cells are shipped and delivered on a date that can avoid the immediate impact.

"Storms and natural disasters outside of a typical day-to-day operation really do put a lot of roadblocks in the way of successfully collecting and delivering fresh cells in certain parts of the country," Narr added. "There have been urgent situations where the case management team and our partners have absolutely relied on the capabilities of the cryopreservation service to manage and protect these cells for the patient in light of these natural disasters. It reiterates the importance of the offering in general to the community."

Looking ahead, Narr said she hopes the conversation around cryopreservation focuses more on impact than volume.

"The conversation around growth and increase is important. But it's just as important for our community to proactively create an effective alternate path that's established and available during heightened and urgent situations to prevent scrambling," Narr told *AABB News*. "Being proactive for patients and donors and protecting the product through cryopreservation service is extremely valuable regardless of the volume. Each product is critical to patient care." ■

REFERENCES

1. Devine, S, Bo-Subait, S, Kuxhausen, M, et. Al. Clinical impact of cryopreservation of allogeneic hematopoietic cell grafts during the onset of the COVID-19 pandemic. Blood Advances. 2023; 7 (19): 5982–5993. doi: https://doi.org/10.1182/bloodadvances.2023009786
2. Worel, N., Ljungman, P., Verheggen, I.C.M. et al. Fresh or frozen grafts for allogeneic stem cell transplantation: conceptual considerations and a survey on the practice during the COVID-19 pandemic from the EBMT Infectious Diseases Working Party (IDWP) and Cellular Therapy & Immunobiology Working Party (CTIWP). Bone Marrow Transplant. 2023. https://doi.org/10.1038/s41409-023-02099-w
3. Valentini CG, Pellegrino C, Teofili L. Pros and Cons of Cryopreserving Allogeneic Stem Cell Products. *Cells*. 2024 Mar 21;13(6):552. doi: 10.3390/cells13060552. PMID: 38534396; PMCID: PMC10968795.
4. The National Marrow Donor Program. NMDP Cryopreservation Service. https://network.nmdp.org/services-support/transplant-centers/nmdp-cryopreservation-services
5. Mitchell E. Horwitz; Blood stem cell grafts: frozen is fine, but fresh is best. Blood Adv 2023; 7 (19): 5994–5995. doi: https://doi.org/10.1182/bloodadvances.2023010372