# Cellular collection by apheresis

*Anand Padmanabhan*

Cellular collection is an important and increasingly used apheresis procedure. These collections are performed by leukocytapheresis, a procedure involving the removal of a patient's or donor's white blood cells, and are used to collect hematopoietic progenitor cells, specific cell populations (such as T-lymphocytes), and granulocytes. Hematopoietic progenitor cell apheresis and T-lymphocyte collection are performed by procedures that enrich for mononuclear cells. Hematopoietic progenitor cells are used for autologous and allogeneic hematopoietic stem cell transplantation, whereas T-cell collection is being used increasingly in novel cellular therapy approaches and for donor lymphocyte infusions to induce graft-versus-leukemia effect. Granulocytes are collected from healthy donors to treat severe sepsis in patients who are refractory to antimicrobial therapies. Less frequently, cellular depletion of leukocytes may be indicated in leukemic patients who have severe hyperleukocytosis resulting in leukoaggregation and decreased tissue perfusion. In these procedures, establishing and maintaining adequate vascular access are critical prerequisites to ensuring a successful procedure. For most types of leukocytapheresis procedures, efforts should be made to ensure that they are performed using peripheral veins, and the use of an intravascular access device should be considered only after it is determined that peripheral access is not feasible or desirable. However, in some settings (such as in patients undergoing autologous hematopoietic stem cell transplantation), intravascular access devices are often used to facilitate both the leukocytapheresis procedure and the subsequent transplant. Here, different types of vascular access approaches used in cellular collections are discussed, and this information is supplemented by the author's experience and practice in areas where published information is limited.

Leukocytapheresis is an important type of apheresis procedure with relevance to transplantation and cellular therapy. It may also be used as a therapeutic procedure in select patients. This report seeks to provide the patient context in which leukocytapheresis is performed and discusses key vascular access considerations to facilitate the procedure. The nature of the collection and the needs of the patient often dictate the type of vascular access needed, not only for their leukocytapheresis procedure but also for any additional access needs after the leukocytapheresis has been successfully completed. Below, different types of leukocytapheresis procedures are described followed by a discussion of important considerations related to attaining adequate vascular access to enable safe and effective cellular collections.

## LEUKOCYTAPHERESIS PROCEDURE TYPES

### Mononuclear cell collections

Mononuclear cell (MNC) collection involves the separation and collection of white blood cells enriched for MNCs from whole blood using centrifugation-based techniques. The devices used collect cells either continuously or discontinuously during multiple cycles of collection. Separation and collection of white blood cells are optimized such that MNCs (of which T-cells and cluster of differentiation 34 [CD34]-positive hematopoietic progenitor cells [HPCs] are a subset) are enriched. HPCs are collected for the purpose of autologous or allogeneic transplantation in a variety of mostly

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malignant conditions and some nonmalignant disorders. HPCs are collected from patients and donors after adequate mobilization with growth factors.[1] Donor-derived and patient-derived T-cells are collected for the purpose of novel cellular therapies, such as chimeric antigen receptor T-cell[2] treatment in mostly autologous cellular collections or for inducing a graft-versus-leukemia effect in allogeneic collections. Other cell types of interest in the MNC population are natural killer cells[3] used in some transplant protocols and monocytes used for the preparation of monocyte-derived dendritic cell vaccines.[4] To collect the doses of cells required for these procedures, the necessary volumes of processed blood vary from two to four blood volumes or greater (large-volume leukocytapheresis [LVL]), resulting in a procedure that is several hours in duration.[5] In adults, flow rates typically range from 50 to 90 mL/minute, although rates greater than 100 mL/minute are frequently achieved, especially in the setting of heparin-based anticoagulation. LVL has advantages in that it allows for the collection of a greater number of cells, and this may be especially important in HPC collections from patients with suboptimal mobilization (i.e., those who have a poor response to mobilization agents).

The apheresis devices used to collect MNCs differ somewhat in their hardware specifications and separation technologies but uniformly need good flow rates to process adequate volumes of blood to attain the target dose of cells. Commonly used devices in the United States include the Spectra Optia (Terumo BCT) and the Amicus (Fresenius-Kabi). Due to the proximity of the platelet layer to MNCs, platelet depletion can be a significant clinical concern. The Spectra Optia collects MNCs continually or through cyclical harvest, depending on the protocol used. Figure 1A depicts the continuous MNC method of collection. The Amicus operates through intermittent collection of MNCs, as shown in Figure 1B.

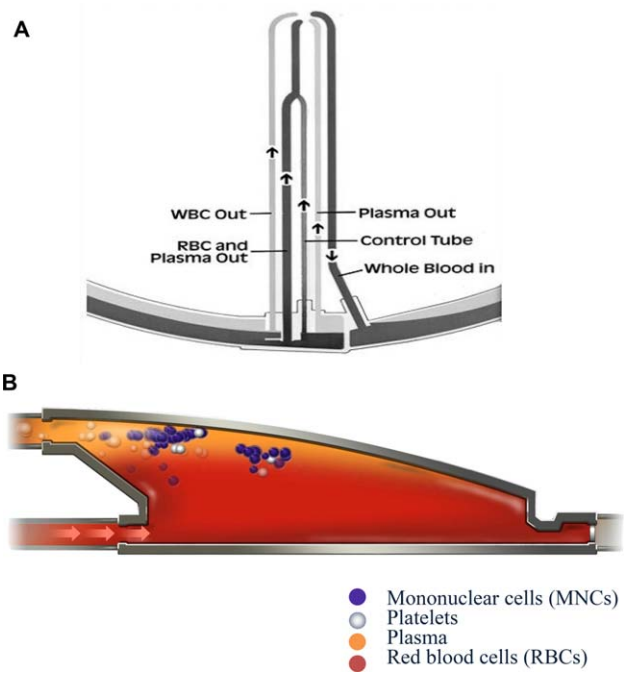


**Fig. 1. MNC collection methodology is illustrated for (A) continuous collection (Spectra Optia; Terumo BCT) and (B) cyclical harvest (Amicus; Fresenius-Kabi). In A, whole blood entering the centrifuge is subject to a soft spin resulting from the packing of RBCs along the high-gravity wall, on top of which are the WBC layer (buffy coat), platelets, and plasma. The buffy coat is continuously removed. In B, during a cycle, whole blood enters the separation chamber, and RBCs reside along the high-gravity wall, whereas platelets are returned to the patient through the platelet-rich plasma outlet. To trigger harvest of MNCs, the packed-RBC outlet closes, and a small volume of RBCs is pumped into the chamber to lift and transfer MNCs through the plasma-rich plasma outlet into a collection bag. This cycle is repeated several times during the HPC collection procedure illustrated in B. Reproduced with permission from Terumo BCT and Fresenius-Kabi USA.**

## Granulocyte collections

There is limited evidence in support of granulocyte transfusion therapy in neutropenic septic patients who are unresponsive to antimicrobial therapies.[6,7] In this procedure, a healthy donor is stimulated either with dexamethasone or growth factor (granulocyte-colony stimulating factor) or both followed by leukocytapheresis.[6] Technically, this differs from MNC collections in that a much darker product is targeted due to the proximity of granulocytes to red blood cells in the centrifuge bowl. This results in a product with high hematocrit (target 7.5%) and varying levels of MNC components. Hydroxyethyl starch 6%, a sedimenting agent, is often used in these collections to enhance yield.[8] In the United States, the Spectra Optia and the COBE Spectra have been used for granulocyte collections.

## White blood cell depletions

Hyperleukocytosis, as observed in patients with acute leukemia, can result in leukostasis, microvascular aggregation, and resultant lack of tissue perfusion. Patients with blast counts in excess of $100{,}000 \times 10^9$/L may be particularly at risk. The American Society for Apheresis classifies use of leukocytapheresis in the setting of leukostasis as a Category II indication (first-line therapy), while prophylactic use of leukocytapheresis in hyperleukocytosis in the absence of leukostasis symptoms is a Category III indication (the optimum role of apheresis therapy is not established; decision making should be individualized).[9]

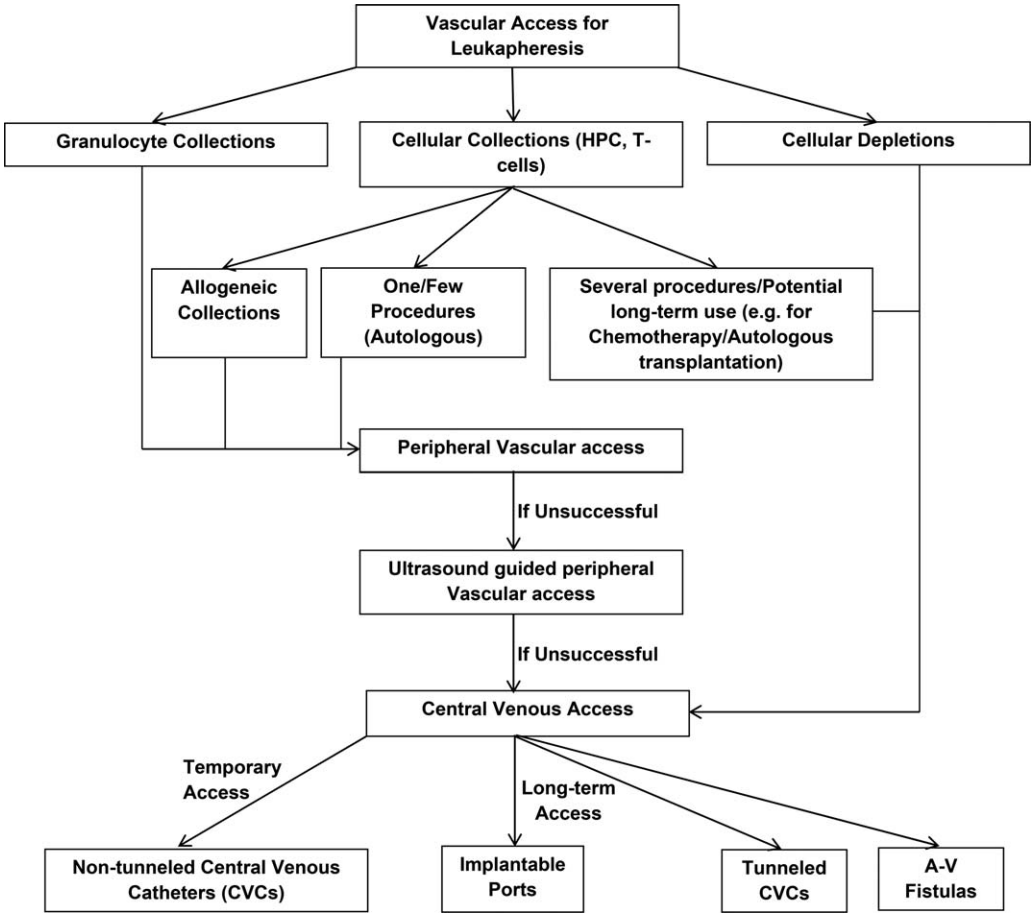


**Fig. 2. The author's approach to vascular access for leukocytapheresis is shown.**

## VASCULAR ACCESS FOR CELLULAR COLLECTIONS

### General considerations

Cellular collections require steady blood flow that can enable the processing of two to four or more blood volumes to collect the desired target cell components. There are several considerations for optimal vascular access in cellular collections (Fig. 2). In the most common type of cellular collections, the collection of HPCs and T-cells, in addition to adequacy of veins, access choice depends on the need for central access for other purposes, such as chemotherapy infusions. In allogeneic donors, the leukocytapheresis procedure is being performed solely for the recipient's benefit, and every effort should be made to minimize risks to the donor. Risks related to intravascular access devices (discussed below), in addition to adverse effects related to leukocytapheresis, are important considerations. At the author's institution, peripheral venous access is evaluated for all allogeneic HPC and T-cell donors, with central access used only in those deemed to have inadequate veins or other contraindications (e.g., donor choice due to severe fear of needle sticks). Among autologous donors, the use of a central venous access device may also facilitate interventions after the completion of leukocytapheresis, such as infusion of chemotherapeutic drugs and HPCs. Thus, the choice of access in autologous donors needs to be made on a case-by-case basis after taking these considerations into account. Programs vary widely in their use of peripheral blood CD34-positive cell counts before leukocytapheresis to optimize HPC collections and in the targeted dose of CD34-positive cells to be collected.[10] Thus, the number of days of collection can vary from 1 to several (3-5) days, depending on mobilization status, disease type, and cell yield goals. At the author's institution, a data-driven "prediction" algorithm is in place in which highly mobilized patients and donors have their LVL procedures truncated based on a prediction of adequate cellular yields (unpublished results). The use of this protocol results in the truncation of roughly one-half of all adult allogeneic and pediatric autologous HPC collections and of approximately 10% of adult autologous collections. The choice of central access may be important in the setting of LVL, because it allows for faster processing of blood and earlier completion of

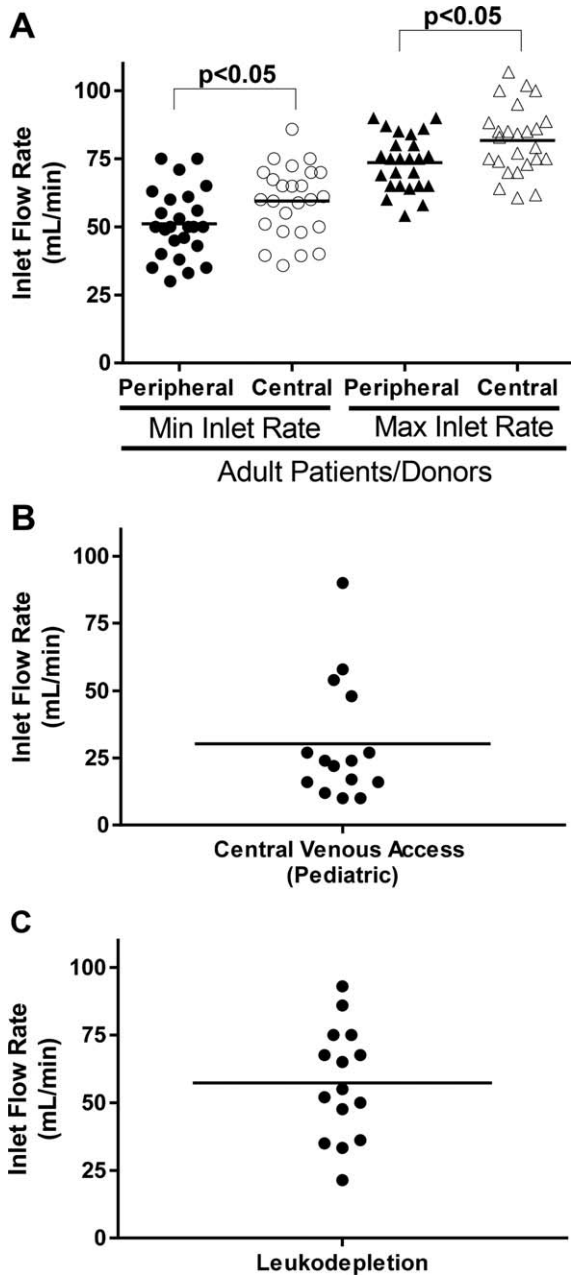


**Fig. 3. (A) Minimum and maximum apheresis inlet flow rates in 20 recent adult HPC donors with peripheral and central venous access are depicted. (B) Inlet flow rates in 15 pediatric HPC donors with central venous access and (C) an equal number of patients undergoing leukodepletion procedures are shown. Horizontal lines indicate mean values. Data presented are from cellular collections at the author's institution.**

procedures. Figure 3A illustrates the minimum and maximum attained inlet flow rates at the author's institution among peripherally and centrally accessed HPC collections in adults. In this analysis, minimum and maximum apheresis inlet flow rates were abstracted from the procedure record, and "average" flow speeds were calculated using these entries. The average inlet flow rates in peripheral versus central access among adult HPC collections were 62 versus 71 mL/minute ($p < 0.05$). In addition, minimum and maximum flow rates were significantly lower in peripherally accessed individuals at 51 versus 59 mL/minute and 74 versus 82 mL/minute, respectively. Central venous access is also typically used in pediatric collections because of the patient's small size and difficulty in maintaining adequate flow with needles. Inlet flow rates with central access among pediatric collections are illustrated in Figure 3B. Flow rates vary widely in this population because of large differences in body size and, consequently, blood volumes, from one child to another. Granulocyte collections, as cellular collections from healthy donors, should always be performed using peripheral access (Fig. 2) to eliminate the risks associated with central venous access devices. Cellular depletions, on the other hand, are unlikely to be performed successfully using peripheral access in a patient who has high white blood cell or blast counts and hyperviscosity (Fig. 2). Thus, central venous access devices are almost universally utilized to facilitate leukodepletions. Typically, one to three leukodepletion procedures are performed in a given patient. At the author's institution, among 15 recent procedures, 12 patients (80%) received only one leukodepletion, whereas three (20%) received two procedures. Average flow rates were modest at less than 60 mL/minute because of hypercellularity or viscosity despite the use of central venous access (Fig. 3C). In cellular collections, when central venous access is not desirable or feasible, peripheral access to enable leukocytapheresis should be explored. Peripheral access and various types of central venous access are discussed below.

## Peripheral venous access

Patient evaluation should begin with a detailed assessment of peripheral vein location and size. In patients with adequate peripheral venous access, large-bore needles (typically, 16-18 gauge [G]) are utilized for draw and return of blood to the donor. Challenges with peripheral access are often encountered in small and overweight/obese individuals. Many programs reserve the use of central vascular access for such patients/donors.

Important considerations for peripheral vascular access include:

1. The use of warmers to dilate peripheral vessels,
2. Well hydrated patients/donors,
3. The patient should be able to remain in a supine position with an outstretched arm (if antecubital access) for prolonged periods of time, and
4. Well trained staff with experience in venous cannulation using large-bore needles.

At the author's center, 17G and 18G arteriovenous fistula needles are typically used for access. 18G intravenous catheters also may be used for return flow for settings in which there is concern about the vein's ability to tolerate a straight arteriovenous fistula needle. Several groups have demonstrated that even in settings where peripheral access is initially deemed challenging, successful cannulation may be achieved with the help of ultrasound point-of-care devices.[11,12] Thus, ultrasound-guided cannulation of veins greater than 3 or 4 mm in subcutaneous depth can be achieved successfully.[13] In one study, cannulation was performed successfully in more than 40 HPC collections[12] and the success rate of ultrasound-guided peripheral venous access appears to be high at approximately 85% in a second study (71 of 84 procedures).[11] Veins frequently accessed include the basilic, brachial, and cephalic veins in the upper arm; basilic and median cubital veins in the antecubital fossa; and cephalic and radial veins in the lower arm.[11]

## Central venous access: Catheters and implantable ports

### *Temporary access*

In instances where peripheral access is deemed inadequate or undesirable, options include the placement of temporary or long-term access devices, depending upon need. If access is desired solely for the purpose of facilitating one or a few cellular collections, then a non-tunneled central venous catheter (CVC) (e.g., Mahurkar catheters; Medtronic Inc.) is used. The size of the catheter depends on body size. 10 to 13.5-French catheters should be able to accommodate a variety of body sizes; however, for patients lighter than 20 kilograms, 7-French or 8-French catheters may be indicated. Catheter locations are most commonly in the internal jugular, subclavian, or femoral veins, and institutional-specific preferences often guide placement location. Although infrequent, femoral access has been used successfully for HPC collections[14] and is often used in the setting of emergent leukodepletion in leukemic patients with hyperleukocytosis. The risk of central venous stenosis is considered to be higher with the use of subclavian access.[15,16] Femoral CVCs, on the other hand, are associated with a greater risk of infection.[17] Placement of these catheters should be image-guided to minimize the risk of malpositioning and related complications.[18] Catheters should be securely sutured, and the apheresis practitioner should carefully evaluate the exit site for oozing, bleeding, and discharge before every use. Because infection is a risk in every patient, especially those with central access, the patient should be monitored closely for signs and symptoms of infection, including fevers and chills. Other risks with CVCs include pneumothorax, catheter thrombosis, bleeding, and vessel puncture.[19]

Hospital policies vary in their protocols related to the service used for placing CVCs, catheter capping, and catheter maintenance. In a recent survey of 100 centers performing cellular collections, the interventional radiology service inserted the majority of catheters for both autologous and allogeneic donors.[20] Most centers used heparin to cap catheters but differed significantly in the concentration of heparin used. Surprisingly, citrate or saline was used only in 8% and 10% of centers, respectively, for autologous donors. Tissue plasminogen activator is frequently used by centers to address catheter thrombosis, which most perform as an instillation for up to 1 hour.[20]

### *Long-term access*

**Tunneled CVCs.** In many cases, especially among individuals who donate HPCs for autologous hematopoietic stem cell transplantation, long-term vascular access that can be used for both cellular collection and medication administration (e.g., chemotherapy) is desired. In this type of access, the catheter is placed through a subcutaneous tunnel before accessing the large central vein. These catheters have a "cuff," which allows tissues to granulate effectively "anchoring" the catheter.[21] Tunneled CVCs have the advantage of being more secure, and less prone to infection than temporary CVCs. Despite this, tunneled CVCs can and do have complications as evidenced by less than 50% of catheters in place 1 year after initiation of a common procedure akin to apheresis, dialysis.[22] An example of a tunneled central venous catheter that may be used for cellular collections is the Hickman Trifusion catheter (Bard Inc.).

**Tunneled CVCs-ports.** Another option for long-term access is the placement of subcutaneous port-CVCs. Port-CVCs are subcutaneous access devices connected to polyurethane or silicone catheters that provide access to a large central vein. The port itself is placed in a pocket in the subcutaneous tissue anteriorly on the chest wall. The devices can be either single or double lumen, and experience suggests that they can be used effectively for apheresis therapy. The Vortex port (Angiodynamics Inc.) has been used for both red blood cell exchange procedures and extracorporeal photopheresis, and it can attain inlet speeds of up to 40 to 50 mL/minute.[23,24] Like other types of access, thrombosis can be a concern, necessitating the use of a tissue plasminogen activator for clot dissolution.[24] Another port that has been used previously (but is not currently available) is the CathLink 20 (Bard Inc.). This port has been used for both plasma and red blood cell exchange procedures with a mean access flow rate of 70 mL/minute.[25-27] Although data on the use of these ports for cellular collections are limited, it is not unreasonable to expect that data in this area will increase, especially with the availability of the PowerFlow port (Bard Inc.) the design of which is based on its predicate device (the CathLink 20) and was recently approved by the US Food and Drug Administration for use in apheresis.[28] Because this is a single-lumen port, either two ports need

**TABLE 1. Settings, advantages, and disadvantages of various vascular access types in leukocytapheresis***

| Access type | Setting | Advantages | Challenges |
|---|---|---|---|
| Peripheral veins | Adequate veins; one or few procedure(s) anticipated | No complications related to CVCs | Hematoma, hands outstretched for prolonged period (if antecubital vein access); ultrasound point of care devices not always available |
| Non-tunneled CVCs | Veins not adequate; one or few procedure(s) anticipated | Supports high flow rates (>100 mL/min); faster completion of procedure | Risks associated with CVCs, infection, thrombosis, catheter displacement/bleeding |
| Tunneled CVCs | Veins not adequate; several procedures anticipated; potential long-term (weeks/months) use (e.g., for chemotherapy) | Supports high flow rates (>100 mL/min); faster completion of procedure; lesser likelihood of infection/displacement relative to non-tunneled CVCs | Risks associated with tunneled CVCs, infection, thrombosis |
| Port-CVCs | Veins not adequate; several procedures/weeks-months of access anticipated | Flow rates vary by device; cosmetically, less displeasing than CVCs; lesser likelihood of infection/displacement | Infection, thrombosis; sometimes breast tissue in females makes access difficult and painful |

* Arteriovenous fistulae/grafts are not discussed here because of their rarity in this setting.

to be implanted or, if a single port is placed, then it should be used for drawing blood into the apheresis device, and a peripheral vein used to return blood to the patient. In vitro testing by the manufacturer suggests that flow rates of up to 150 mL/minute may be achieved; however, data from in-human use are currently limited. Rates of infection with ports are typically low. In one large study of 700 patients, 4% of infections were attributed to port-related causes.[29] To ensure the longevity of port diaphragms, either noncoring needles or specialized needles recommended by the port manufacturer should be used.

### *Other: Arteriovenous fistula/graft*

Arteriovenous fistulae have been used extensively for vascular access in dialysis, and this type of access also has been used successfully in patients undergoing apheresis.[30,31] This is a particularly common type of access for therapeutic plasma exchange among patients who have had arteriovenous fistulae/grafts placed previously to facilitate hemodialysis. Despite the dearth of literature describing their use in cellular collections, they support high flow rates and theoretically could be used in this setting. Of note, not all apheresis personnel are trained in fistula/graft access, and enhancement of skills in this area is required before successful cannulation. Often, patients themselves provide key information on the optimal location of needle placement, having experienced access repeatedly to facilitate hemodialysis. The use of any type of vascular access has advantages and limitations. These are detailed in Table 1.

## CONCLUSION

Cellular collections are a rapidly expanding area of apheresis. Hematopoietic stem cell transplantation is being used to treat malignant and nonmalignant conditions, and novel cellular therapies are being considered definitive therapy for several cancers. To facilitate these procedures, the choice of vascular access is critical. Several factors, including adequacy of peripheral veins, medication administration needs of the patient, duration and frequency of procedures, and skills of the apheresis team should be taken into careful consideration before vascular access decisions are made. It is likely that with refinement of protocols and the expansion of cellular therapies for new indications, these decisions will have a significant impact on ensuring safe and effective leukocytapheresis.

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