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REVIEW

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Apheresis collection of mononuclear cells for chimeric-antigen receptor therapies

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Abstract

Collections of lymphocytes to be genetically modified to treat hematologic malignancies have seen a dramatic increase over the last few years as commercial products have been approved. Reports of new products in development that can possibly treat solid organ malignancies represent a massive change in the field. Apheresis is at the center of the collection of cells for the manufacture of these chimeric-antigen receptor therapy products. The expansion of these collections represents one of the areas of apheresis procedures growth. This review will summarize concepts important to this type of collection and variables that need to be optimized to obtain desired cell yields while increasing patients' safety.

KEYWORDS
adverse events, apheresis, CAR T, cell collections, chimeric-antigen receptor therapy, efficiency, variables

Novelty Statement

The beginning of chimeric-antigen receptor therapies has resulted in an increase in the number of apheresis procedures performed to obtain cells for product manufacturing. Apheresis can lead to adverse events due to its invasive nature. This manuscript outlines in a concise manner those variables that must be considered to perform procedures with increased safety. These important areas are discussed separately so that practitioners can proactively prepare for procedures and adjust collections to increase their success with a focus on patient safety.

1 | INTRODUCTION

The war on cancer was declared in the early 1970s and despite many discoveries since, cures or treatments that lead to long remissions have remained mostly elusive. Nevertheless, there is one development over the last decade that may represent a truly "seismic discovery" in the fight against cancer and this is the dawn of chimeric-antigen receptor T cell (CAR T) therapies. Indeed, the literature published outlining results from CAR T clinical trials to hematological malignancies are an indicator that these therapies represent a real opportunity to treat patients with better outcomes. Impressive results from these trials brought about the relatively rapid approval for the therapeutic use of tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) to treat B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma, respectively.[1] This has resulted in the logical increase in studies to expand not only CAR T to other hematological malignancies but also to bridge the gap to address solid organ malignancies as well.[2]

The manufacture of these therapies is at the mercy of the successful collection of a sufficient number of T cells (10^9) by apheresis to send to designated centralized manufacturing facilities to generate these products.[3] These therapies are the result of a number of innovations that have led to several generations of CAR T, with each

generation showing improvements upon the prior ones. These newer CAR T products have improved not only in the specificity of their antigen-binding region but through the expression of co-stimulatory signals and regulatory sequences in the receptor, allowing for better control of signal transduction and response to stimulatory agents such as interleukins that lead to improved proliferation and targeted cell killing.[4]

CAR T therapies are currently limited to treat patients able to donate their own cells for product manufacturing. These CAR T cells either target a single antigen or at most two expressed on malignant cells.[5] Thus, an immediately obvious limitation of these therapies is that they can only be used for the intended recipient and if the patient cannot for one reason or another use the product, cells are of no benefit to any other patient. This is one of the reasons for the push to develop universal CAR T cellular products capable of targeting multiple malignant cell types,[6] including solid tumors.[1] Likewise, research into allogeneic CAR Ts, derived from healthy donors and engineered to express chimeric receptors specific for a tumor-associated antigen and modified through gene-editing so that they can be administered to any patient regardless of major histocompatibility complex represents a promising breakthrough.[7–9] Finally, the recent discovery of a T-cell subpopulation that through its receptor targets and destroys a broad spectrum of malignant cells may provide the cellular template to develop universal products that can target a variety of malignant neoplasms.[10] Thus, the goal of this concise review is to outline variables that must be considered to perform apheresis collection procedures of cells for CAR T manufacturing with increased safety.

2 | CELL COLLECTIONS

2.1 | General considerations

The collection of cells for CAR T manufacturing has markedly increased over the last 4 to 5 years. Apheresis platforms collect these cells by targeting the cellular interface (region containing leukocytes and platelets) through its continuous mononuclear cell collection software which determines cells to be collected based on cell layer densities. These modern platforms use centrifugal forces and readily collect $\geq 1 \times 10^9$ $CD3^+$ lymphocytes efficiently with improved cell viability regardless of chemotherapeutic treatment and patient's age.[11] In the case of platforms such as the Spectra Optia, short procedures run times limit the number of platelets lost to the product unless the operator is forced to adjust collection parameters.[12] Importantly, collections are mostly uneventful even in younger patients with procedure efficiencies well over 80%.[13] However, despite the short duration of these collections, adverse events can occur but these appear to be no different in frequency compared to those observed during peripheral blood stem cell (PBSC) collections.

One of the most contentious topics in the field is the timing of collection to achieve a successful yield that allows for product manufacture. Currently, counts are obtained using flow cytometry before or on the day of collection to establish the length of collection based on liters of blood to be processed. Since flow cytometric results take time, collections are either delayed pending flow results or begin without having counted to determine the likelihood of success. This has led to the development of prediction models which take into account, parameters such as counts, time on the machine, and volume to be processed to establish if the procedure should be undertaken.[14] Importantly, as for PBSC collections, parameters such as high hematocrit, higher peripheral $CD3^+$ count and platelet count in the normal range determine not only a procedure's efficiency but establish the number of liters needed to be processed to achieve a cell yield.[14] If one or more of these variables are low they will need to be improved through transfusions of red blood cells (RBCs) or platelets to optimize collection efficiency.

Collections for transplant or manufacture represent one of the safest apheresis procedures,[15] however, rare serious adverse events have been reported which is not uncommon from an invasive procedure.[16–18] Nevertheless, if preparation for donation is undertaken well in advance of collection, the safety of the procedure is increased.[19] This is especially true of pediatric collections since apheresis system parameters are not designed for small-weight patients, specifically young children.[20,21] This is because the extracorporeal volume (ECV) is proportionately of increasing significance the smaller the patient, so preparation for collections needs to optimize hematocrit, electrolytes and prepare for fluid shifts among variables to monitor in such patient population.[22] In these procedures, priming of the circuit with a unit of blood maintains the patient's initial hematocrit minimizing ECV changes affecting young children; at the same time decreasing the inlet while lowering the flow speed once you enter patient's weight into the system will limit the blood volumes that can be processed during a procedure run.[23]

2.2 | Procedure duration

Long procedures lead to significantly greater platelet losses in the product.[24] New machines collect cells with lower platelet removal compared to older platforms due to their higher efficiency per liter of blood processed,[25,26] diminishing the need for long collections to obtain higher cell numbers per procedure run.[27] This lower platelet removal is particularly important for patients who, because of their disease state or therapy, have platelet counts in the low or low-normal range at the start of collection.[28,29] Despite technological advances, machines still allow for the operator to adjust preferences to reduce further RBC contamination or to improve when necessary collection yield when cell counts are relatively small.[30–32] This is something that is facilitated by the platform's software management system.[33] Even though this could be seen as leading to every collection being modified by the operator, this is not the case since greater contamination by other cell types of the product can occur in this way requiring additional manipulation and processing of the product including collection of additional plasma to aid in cryopreservation.[28]

Collections can be accomplished even when patients are as small as 8 kg through greater systems' efficiency despite processing fewer

liters of blood per procedure run.[34,35] As mentioned above, blood priming when prompted by a machine, intravenous calcium supplementation and monitoring, and sedation, can result in uneventful procedures.[36] Importantly, since collections of cells for CAR T manufacture require a single procedure, the number of expected adverse events is low since these tend to occur with greater frequency when multiple days of collection are needed as seen in PBSC collections.[37] As a result, the duration of a collection is one of the most important factors determining the occurrence of adverse events.[29,38] This is particularly apparent when comparing newer efficient machines to older platforms that required longer procedures.[30,38–40]

2.3 | Vascular access

Central venous access is at times preferred to perform procedures fast and to process a greater number of liters of blood during a collection. The propensity of vascular collapse under the stress of negative pressures generated by apheresis platforms limits the use of small veins or veins of small patients that need to be accessed with large bore needles required for apheresis, which may favor the placement of central access.[21] Catheter placement has inherent risks that should be minimized whenever possible. Collection of cells for CAR T manufacturing is performed mostly during a single procedure thus these collections can be attempted using peripheral vascular access and if patients can sit still for several hours. Peripheral venous catheters can also be used since their placement under ultrasound guidance avoids difficulties associated with other forms of access.[41] Very rarely there is the placement of femoral central catheters due to their reported higher infection rates compared to access placed in the jugular or subclavian vessels, however, these may be overstated in the literature.[42,43] Importantly, when central lines are needed because of poor vasculature of the patient, infection risks may not be applicable since catheters remain only for the duration of collection and are removed soon after completion of the procedure.[44,45]

2.4 | Calcium optimization

The apheresis system utilizes anticoagulant citrate dextrose solution, solution A (ACD-A), a calcium chelator that can lead to hypocalcemia. In children, this may go unnoticed due to sedation or inability to verbalize symptoms,[46,47] making calcium optimization the single most important electrolyte to manage during collections. Development of hypocalcemia secondary to ACD-A is of particular concern for patients characterized by small weight and/or size due to smaller calcium reserves, or those who have a preexisting condition in which low calcium can lead to significant complications.[48–50] Most hypocalcemia symptoms are characterized by paresthesias, headaches, nausea, vomiting, and only in the most serious situations intense spasms and arrhythmias.[51] These reactions can be resolved by decreasing the inlet so that the amount of ACD-A is reduced and by providing oral calcium supplementation to improve symptomatology. For patients who are intubated, sedated, or who did not improve with oral calcium, intravenous calcium can be given for symptom relief and maintained through the collection.[52] The importance of maintaining ionized calcium at or above the normal range is indicated by the few adverse events otherwise encountered during collections when calcium is optimized.[53,54]

2.5 | RBC mass

It may be counterintuitive but improving red cell mass favors better leukocyte collection yields by apheresis. The reason for this is that red cell mass influences the stability of cell layers formed during centrifugation through the ability of RBCs to exclude water as they are packed together by centripetal forces leading to well-defined layers. This is readily apparent by the optimal efficiency seen in collections with hematocrits ≥35%,[55] while hematocrits <30% lead to longer times until formation of the interface, and lower procedure efficiency and stability of the interface.[56,57] Likely, higher hematocrit is not an option in sickle cell disease patients due to viscosity concerns and in this population, the hematocrit should be targeted to be not greater than 30% to minimize complications.[58] Another benefit of improving the hematocrit before collection is that blood priming would not be needed in adult patients, and in those individuals whose lymphocyte counts are low to borderline, the higher efficiency may represent the best opportunity for collecting the greatest number of cells for product manufacture.

2.6 | Adverse events and safety

The vast number of collections are performed in the outpatient setting due to the overall safety of apheresis collections.[15,59] In patients or allogeneic donors who because of age (young children) require sedation, procedures may be done in the intensive care setting to monitor for vital signs, ionized calcium, and sedative dosing.[60] In those patients with comorbidities such as prior cardiac history, they may need to be monitored in an inpatient setting to improve safety and proactively prepare for complications if they were to arise. If this is not possible, cardiac monitoring and calcium supplementation are recommended to decrease the possibility that hypocalcemia leads to adverse cardiac events in this patient group. Consequently, most adverse events in collections would fall into three categories: hypocalcemia, central access-related problems such as bleeding or thrombosis, and those that are technical in nature.[61]

2.7 | CAR T production challenges

The beginning of CAR T therapies has been characterized by a lack of standardization. Available commercial products utilize their own systems from T-cell isolation to in vitro cell expansion that lack uniformity. Apheresis collection represents the common variable and is likely the uniform step in the manufacturing process. Lack of

standardization is readily apparent when considering the variety of culture systems currently used in the manufacturing process.[62] Similarly, there is heterogeneity in flow cytometric and polymerase chain reaction-based methodologies used to detect CAR T cells post-infusion and establish how frequently they are used.[63] However, the implementation of mass production steps seeking uniformity for therapies that are inherently examples of personalized precision medicine will represent a continuous challenge in the field.[64]

3 | CONCLUSION

The dawn of CAR T therapies is the reason for optimism that hematologic neoplasms will have better outcomes as cell therapy products are improved. Without a doubt, once products are developed to treat solid tumors a new era in the war on cancer will have begun. Apheresis collection of cells for CAR T manufacture will likely continue to grow and a proactive vigilant approach to collections that prepares to minimize the occurrence of adverse events will further improve safety as the number of products expand.

AUTHOR CONTRIBUTION

Robert W. Maitta is the sole author of this manuscript.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

This is a concise review and all data is as referenced in the text.

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REFERENCES

1. Ma S, Li X, Wang X, et al. Current progress in CAR-T cell therapy for solid tumors. *Int J Biol Sci*. 2019;15(12):2548-2560.
2. Sermer D, Brentjens R. CAR T-cell therapy: full speed ahead. *Hematol Oncol*. 2019;37(suppl 1):95-100.
3. Morgan RA, Gray D, Lomova A, Kohn DB. Hematopoietic stem cell gene therapy: progress and lessons learned. *Cell Stem Cell*. 2017;21(5):574-590.
4. Zhao J, Lin Q, Song Y, Liu D. Universal CARs, universal T cells, and universal CAR T cells. *J Hematol Oncol*. 2018;11(1):132.
5. Ruella M, Barrett DM, Kenderian SS, et al. Dual CD19 and CD123 targeting prevents antigen-loss relapses after CD19-directed immunotherapies. *J Clin Invest*. 2016;126(10):3814-3826.
6. Jo S, Das S, Williams A, et al. Endowing universal CAR T-cell with immune-evasive properties using TALEN-gene editing. *Nat Commun*. 2022;13(1):3453.
7. Qasim W. Allogeneic CAR T cell therapies for leukemia. *Am J Hematol*. 2019;94(s1):S50-S54.
8. Marcus A, Eshhar Z. Allogeneic chimeric antigen receptor-modified cells for adoptive cell therapy of cancer. *Expert Opin Biol Ther*. 2014;14(7):947-954.
9. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. *Nat Rev Drug Discov*. 2020;19(3):185-199.
10. Crowther MD, Dolton G, Legut M, et al. Genome-wide CRISPR-Cas9 screening reveals ubiquitous T cell cancer targeting via the monomorphic MHC class I-related protein MR1. *Nat Immunol*. 2020;21(2):178-185.
11. Harrer DC, Heidenreich M, Fante MA, et al. Apheresis for chimeric antigen receptor T-cell production in adult lymphoma patients. *Transfusion*. 2022;62(8):1602-1611.
12. Putensen D, Smith R, Pilcher L, Trandafir G. Comparison of the CMNC and MNC apheresis protocol for the collection of T-cells showed comparable outcome: an observational study in a single centre. *J Clin Apher*. 2018;33:349-356.
13. Ceppi F, Rivers J, Annesley C, et al. Lymphocyte apheresis for chimeric antigen receptor T-cell manufacturing in children and young adults with leukemia and neuroblastoma. *Transfusion*. 2018;58(6):1414-1420.
14. Jo T, Yoshihara S, Hada A, et al. A clinically applicable prediction model to improve T cell collection in chimeric antigen receptor T cell therapy. *Transplant Cell Ther*. 2022;28(7):365.e1-365.e7.
15. Kundrapu S, Datla S, Griffin V, Maitta RW. Adverse events during apheresis: a 10-year experience at a tertiary academic medical center. *J Clin Apher*. 2019;34(5):528-536.
16. Brauninger S, Bialleck H, Seifried E, Bonig H. Asystole during stem cell apheresis in a young healthy female volunteer donor. *Transfusion*. 2011;51(7):1594-1595.
17. Holig K, Kramer M, Kroschinsky F, et al. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. *Blood*. 2009;114(18):3757-3763.
18. Halter J, Kodera Y, Ispizua AU, et al. Severe events in donors after allogeneic hematopoietic stem cell donation. *Haematologica*. 2009;94(1):94-101.
19. Ohto H. Efficient and safe stem cell apheresis. *Transfus Apher Sci*. 2004;31(3):203-205.
20. Maitta RW. Current state of apheresis technology and its applications. *Transfus Apher Sci*. 2018;57(5):606-613.
21. Empringham B, Chiang KY, Krueger J. Collection of hematopoietic stem cells and immune effector cells in small children. *Transfus Apher Sci*. 2018;57(5):614-618.
22. Maitta RW, Vasovic LV, Mohandas K, Music-Aplenc L, Bonzon-Adelson A, Uehlinger J. A safe therapeutic apheresis protocol in paediatric patients weighing 11 to 25 kg. *Vox Sang*. 2014;107(4):375-380.
23. Gorlin JB, Humphreys D, Kent P, et al. Pediatric large volume peripheral blood progenitor cell collections from patients under 25 kg: a primer. *J Clin Apher*. 1996;11(4):195-203.
24. Ikeda K, Ohto H, Kanno T, et al. Peripheral blood progenitor cell collection by two programs for autologous and allogeneic transplantation. *Transfusion*. 2014;54(5):1235-1242.
25. Drezet A, Granata A, Lemarie C, Calmels B, Chabannon C. An intrapatient comparison of blood cell separators Spectra and Optia in patients and donors undergoing blood mononuclear cell collections at a single institution for subsequent autologous or allogeneic hematopoietic cell transplantation reveals comparable collection efficiencies. *Bone Marrow Transplant*. 2016;51(7):1007-1009.
26. Lee SN, Sohn JY, Kong JH, Eom HS, Lee H, Kong SY. Comparison of two apheresis systems of COBE and Optia for autologous peripheral blood stem cell collection. *Ann Lab Med*. 2017;37(4):327-330.
27. Wuchter P, Hundemer M, Schmitt A, et al. Performance assessment and benchmarking of autologous peripheral blood stem cell collection with two different apheresis devices. *Transfus Med*. 2017;27(1):36-42.
28. Brauninger S, Bialleck H, Thorausch K, Felt T, Seifried E, Bonig H. Allogeneic donor peripheral blood "stem cell" apheresis: prospective comparison of two apheresis systems. *Transfusion*. 2012;52(5):1137-1145.

29. Li Y, Li J, Reeves HM, Reyes R, Maitta RW. Comparison of two apheresis systems during hematopoietic progenitor stem cell collections at a tertiary medical center. *Transfusion*. 2016;56(11):2833-2838.
30. Ikeda K, Ohto H, Nemoto K, et al. Collection of MNCs and progenitor cells by two separators for PBPC transplantation: a randomized crossover trial. *Transfusion*. 2003;43(6):814-819.
31. Knudsen LM, Nikolaisen K, Gaarsdal E, Johnsen HE. Kinetic studies during peripheral blood stem cell collection show CD34+ cell recruitment intra-apheresis. *J Clin Apher*. 2001;16(3):114-119.
32. Heuft HG, Dubiel M, Rick O, Kingreen D, Serke S, Schwella N. Inverse relationship between patient peripheral blood CD34+ cell counts and collection efficiency for CD34+ cells in two automated leukapheresis systems. *Transfusion*. 2001;41(8):1008-1013.
33. Sanderson F, Poullin P, Smith R, et al. Peripheral blood stem cells collection on Spectra Optia apheresis system using the continuous mononuclear cell collection protocol: a single center report of 39 procedures. *J Clin Apher*. 2017;32(3):182-190.
34. Cherqaoui B, Rouel N, Auvrignon A, et al. Peripheral blood stem cell collection in low-weight children: retrospective comparison of two apheresis devices. *Transfusion*. 2014;54(5):1371-1378.
35. Sorensen J, Jarisch A, Smorta C, et al. Pediatric apheresis with a novel apheresis device with electronic interface control. *Transfusion*. 2013;53(4):761-765.
36. Greze V, Rouel N, Rochette E, et al. Peripheral blood stem cell collection in children with extremely low body weight (≤8 kg). What have we learned over the past 25 years and where are the limits? *J Clin Apher*. 2021;36(3):322-331.
37. Spinola A, Ferreira S, Amado F, Lopes S, Roncon S. Hematopoietic progenitor cells collection in pediatric patients with brain tumor. *J Clin Apher*. 2016;31(1):22-28.
38. Flommersfeld S, Bakchoul T, Bein G, Wachtel A, Loechelt C, Sachs UJ. A single center comparison between three different apheresis systems for autologous and allogeneic stem cell collections. *Transfus Apher Sci*. 2013;49(3):428-433.
39. Moog R. Apheresis techniques for collection of peripheral blood progenitor cells. *Transfus Apher Sci*. 2004;31(3):207-220.
40. Reinhardt P, Brauninger S, Bialleck H, et al. Automatic interface-controlled apheresis collection of stem/progenitor cells: results from an autologous donor validation trial of a novel stem cell apheresis device. *Transfusion*. 2011;51(6):1321-1330.
41. Soderstrom A, Norgaard MS, Thomsen AE, Sorensen BS. Ultrasound-guidance of peripheral venous catheterization in apheresis minimizes the need for central venous catheters. *J Clin Apher*. 2020;35(3):200-205.
42. Marik PE, Flemmer M, Harrison W. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: a systematic review of the literature and meta-analysis. *Crit Care Med*. 2012;40(8):2479-2485.
43. Arvaniti K, Lathyris D, Blot S, Apostolidou-Kiouti F, Koulenti D, Haidich AB. Cumulative evidence of randomized controlled and observational studies on catheter-related infection risk of central venous catheter insertion site in ICU patients: a pairwise and network meta-analysis. *Crit Care Med*. 2017;45(4):e437-e448.
44. Cooling L, Hoffmann S, Webb D, Yamada C, Davenport R, Choi SW. Performance and safety of femoral central venous catheters in pediatric autologous peripheral blood stem cell collection. *J Clin Apher*. 2017;32(6):501-516.
45. Moreiras-Plaza M, Albo C, Ares C. Efficacy and safety of femoral vascular access for peripheral blood stem cell (PBSC) collection. *Bone Marrow Transplant*. 2004;33(3):347-350.
46. Sauer H, Roland H, Ulla L, Ortrud D, Jurgen F. Leukapheresis in children weighing less than 20 kg. *Pediatr Blood Cancer*. 2012;58(4):627-629.
47. Salazar-Riojas R, Garcia-Lozano JA, Valdes-Galvan M, et al. Effective collection of peripheral blood stem cells in children weighing 20 kilogram or less in a single large-volume apheresis procedure. *J Clin Apher*. 2015;30(5):281-287.
48. Hegde V, Setia R, Soni S, et al. Prophylactic low dose continuous calcium infusion during peripheral blood stem cell (PBSC) collections to reduce citrate related toxicity. *Transfus Apher Sci*. 2016;54(3):373-376.
49. Buchta C, Macher M, Bieglmayer C, Hocker P, Dettke M. Reduction of adverse citrate reactions during autologous large-volume PBPC apheresis by continuous infusion of calcium-gluconate. *Transfusion*. 2003;43(11):1615-1621.
50. Yuan S, Ziman A, Smeltzer B, Lu Q, Goldfinger D. Moderate and severe adverse events associated with apheresis donations: incidences and risk factors. *Transfusion*. 2010;50(2):478-486.
51. Brunner-Spiering JD, Grootes ME, te Boekhorst PA, de Greef GE. Does standard intravenous calcium gluconate administration during peripheral blood stem cell collection reduce the chance of a citrate reaction? *Transfus Apher Sci*. 2013;48(2):199.
52. Adamski J, Griffin AC, Eisenmann C, Milone MC, Sachais BS. Increased risk of citrate reactions in patients with multiple myeloma during peripheral blood stem cell leukapheresis. *J Clin Apher*. 2010;25(4):188-194.
53. Fujii K, Fujii N, Kondo T, et al. Effectiveness of supplemental oral calcium drink in preventing citrate-related adverse effects in peripheral blood progenitor cell collection. *Transfus Apher Sci*. 2021;60(4):103147.
54. Kishimoto M, Ohto H, Shikama Y, Kikuta A, Kimijima I, Takenoshita S. Treatment for the decline of ionized calcium levels during peripheral blood progenitor cell harvesting. *Transfusion*. 2002;42(10):1340-1347.
55. Pornprasertsud N, Niparuck P, Kidkarn R, et al. The use of hematocrit level for predicting the efficiency of peripheral blood $CD34^+$ cell collection after G-CSF mobilization in healthy donors. *J Clin Apher*. 2015;30(6):329-334.
56. Kondo T, Fujii N, Fujii K, et al. Low hematocrit reduces the efficiency of $CD34^+$ cell collection when using the Spectra Optia continuous mononuclear cell collection procedure. *Transfusion*. 2022;62(5):1065-1072.
57. Pham HP, Dormesy S, Wolfe K, Budhai A, Sachais BS, Shi PA. Potentially modifiable predictors of cell collection efficiencies and product characteristics of allogeneic hematopoietic progenitor cell collections. *Transfusion*. 2021;61(5):1518-1524.
58. Sharma A, Leonard A, West K, et al. Optimizing haematopoietic stem and progenitor cell apheresis collection from plerixafor-mobilized patients with sickle cell disease. *Br J Haematol*. 2022;198(4):740-744.
59. Kindwall-Keller T. Peripheral stem cell collection: from leukocyte growth factor to removal of catheter. *J Clin Apher*. 2014;29(4):199-205.
60. Karakukcu M, Unal E. Stem cell mobilization and collection from pediatric patients and healthy children. *Transfus Apher Sci*. 2015;53(1):17-22.
61. Cooling L, Hoffmann S, Webb D, et al. Procedure-related complications and adverse events associated with pediatric autologous peripheral blood stem cell collection. *J Clin Apher*. 2017;32(1):35-48.
62. Mizukami A, Swiech K. Platforms for clinical-grade CAR-T cell expansion. In: Swiech K, Malmegrim K, Picanço-Castro V, eds. *Chimeric Antigen Receptor T Cells. Methods in Molecular Biology*. Vol 2086. Humana; 2020:139-150.
63. Turicek DP, Giordani VM, Moraly J, Taylor N, Shah NN. CAR T-cell detection scoping review: an essential biomarker in critical need of standardization. *J Immunother Cancer*. 2023;11(5):e006596.
64. Dai X, Mei Y, Cai D, Han W. Standardizing CAR-T therapy: getting it scaled up. *Biotechnol Adv*. 2019;37(1):239-245.

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