Child PGI
Institutional Guidelines
for
Apheresis in Pediatric Patients

By
Department of Transfusion Medicine
Post Graduate Institute of Child Health, Noida, UP

Version 1 (December 2024)

Complied by:

Dr Kriti Batni
Senior Resident,
Transfusion Medicine, PGICH, Noida

Dr Anupa Pokhrel
Assistant Professor,
Transfusion Medicine, PGICH, Noida

Edited and reviewed by:
Dr Satyam Arora
Additional Professor,
Transfusion Medicine, PGICH, Noida

Dr Seema Dua,
Additional Professor and Head,
Transfusion Medicine, PGICH, Noida

Institutional Guidelines for Apheresis in Pediatric Patients

CONTENTS:

Department of Transfusion Medicine, Post Graduate Institute of Child Health, Noida, UP

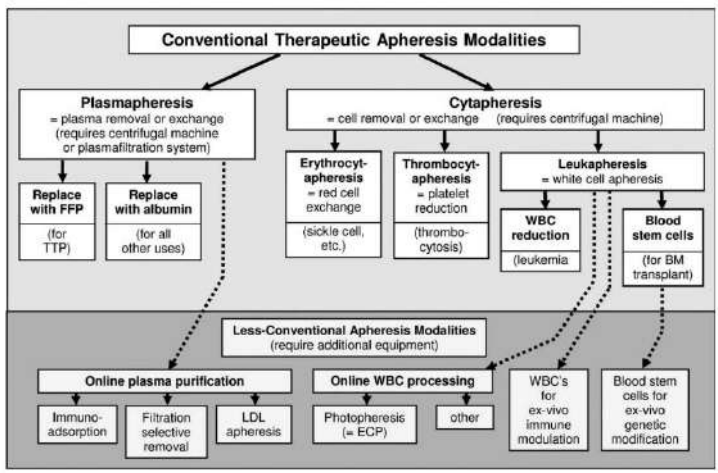
Chapter 1

Introduction to apheresis and Indication of apheresis in Pediatric Patients

Apheresis, derived from the Greek word "aphairesis" meaning "removal," is a medical procedure used to extract specific components from a patient's or donor's blood while returning the remaining blood back into circulation. It is a sophisticated method used to separate and remove targeted blood elements such as plasma, platelets, or white blood cells. In an apheresis procedure, whole blood is drawn from the patient and circulated through an apheresis machine. This device separates and collects specific blood components using centrifugal column technology, while the remaining blood is then safely returned to the donor or patient. The Specific gravity of various blood components are:

- Plasma: 1.026
- Platelets: 1.058
- Monocytes: 1.062
- Lymphocytes: 1.070
- Neutrophils: 1.082
- Red Cells: 1.100

Types of Therapeutic Apheresis (1)



- **Collection/ removal** (including Cytapheresis)
    - Plateletpheresis
    - Plasmapheresis
    - Granulocytapheresis
    - Leukapheresis
    - Erythrocytapheresis
    - Peripheral Blood Stem Cell Apheresis
- **Exchange**
    - Therapeutic Plasma Exchange
    - Therapeutic Red Cell Exchange

Apheresis procedures can be broadly categorized into two main types:

1. **Cytapheresis:** Cytapheresis is a type of apheresis procedure which involves collecting/removing specific components of blood, like platelets or peripheral blood stem cells, from either healthy donors or patients in case of autologous collections. Cytapheresis is commonly done in adult allogenic donors to collect platelets, red cells and granulocytes. In pediatrics, this is commonly seen during stem cell donation, either for autologous (self-donation) or allogeneic (donation to another individual, often a sibling) transplant. Donor apheresis (mainly from adults) is crucial for supporting transplant procedures, especially in children requiring hematopoietic stem cell transplants.

    a) Peripheral Blood Stem Cell Donation: For children with conditions like leukemia, thalassemia, or other hematological disorders, stem cell transplantation is often a curative approach. Apheresis allows the collection of peripheral blood stem cells, which are vital for autologous or allogeneic hematopoietic stem cell transplants (HSCT). Peripheral Blood Stem Cell (PBSC) Collection involves the collection of hematopoietic stem cells (HSCs) from the peripheral blood, which are critical for hematopoietic reconstitution following autologous or allogeneic stem cell transplantation, particularly in oncology patients. In autologous transplantation, HSCs are harvested from the patient while in remission (e.g., in

cases of neuroblastoma or acute lymphoblastic leukemia [ALL]). In allogeneic transplantation, the stem cells are obtained from an HLA-matched donor, typically used for conditions such as leukemia or genetic disorders.

a. Autologous Stem Cell Transplantation: Used in certain types of cancers, such as neuroblastoma or lymphomas, where high-dose chemotherapy is followed by the reintroduction of the patient's own stem cells to repopulate the bone marrow. Indicated in cases of relapsed or refractory cancers requiring aggressive therapy and bone marrow support.
b. Allogeneic Stem Cell Transplantation: Indicated for conditions such as leukemia, severe aplastic anemia, or genetic disorders like thalassemia and sickle cell disease, where healthy stem cells from a matched donor are required to replace the patient's dysfunctional bone marrow. In pediatric settings, apheresis is commonly used for sibling donors.

b) Management of Hematological Disorders by Cellular Reduction: Therapeutic cytapheresis is often employed to remove excess white blood cells (leukapheresis), and platelets (plateletpheresis).

2. **Exchange:** In therapeutic exchange, a specific blood component is removed to treat a medical condition and replaced with a compatible replacement fluid. This is often used in pediatric patients to manage certain diseases or disorders, such as autoimmune conditions, hematological diseases, and metabolic disorders. The procedure helps reduce the burden of pathogenic cells, antibodies, or proteins, helping in disease control or symptom alleviation. Therapeutic exchange apheresis is where the target component (e.g., plasma or red blood cells) is removed and replaced with a healthy donor counterpart.

a) Therapeutic plasma exchange (TPE) is a common procedure in which plasma containing harmful substances (like

autoantibodies or toxins) is removed and replaced with donor plasma or an albumin solution. This is especially useful in treating conditions like autoimmune diseases or certain neurological disorders.

b) Therapeutic red cell exchange (RCE) involves the removal and replacement of abnormal red blood cells (such as sickle cells) with normal red blood cells. This procedure is often used in managing pediatric patients with sickle cell disease to prevent complications like stroke or acute chest syndrome.

    1. Sickle Cell Disease: The primary indication for RCE in pediatric patients is sickle cell disease. This procedure is employed to prevent or manage acute complications, including Stroke prevention in children, Treatment of acute chest syndrome, and management of recurrent pain crises or severe anemia.

    2. Severe Malaria: In rare pediatric cases of severe malaria, RCE can be used to rapidly reduce parasitic load and prevent life-threatening complications like cerebral malaria.

Chapter 2:

Pre-Procedure Phase

The principles of apheresis are similar for both children and adults; however, apheresis equipment is primarily designed for adults, not for infants and young children. To ensure pediatric procedures are conducted safely, it's essential to understand the physical specifications of the equipment. When planning therapeutic apheresis for a child, knowledge of the extracorporeal volume (ECV) of the selected device is crucial, as well as assessing how the ECV might impact the child's total blood volume (TBV) and circulating red cell volume (RCV).

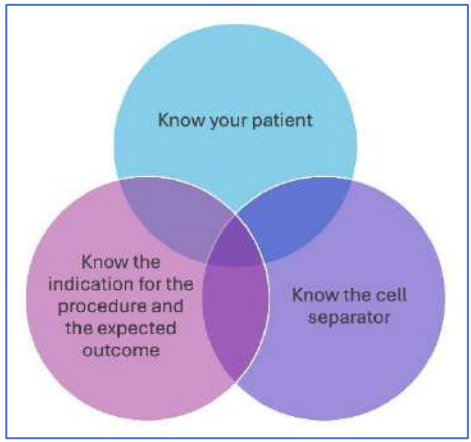


Figure 1: Key to any successful apheresis procedure

The following are the key areas of importance when planning an apheresis procedure in a pediatric age group of patients:

a. Patient Assessment and Indication
b. Consent and Counselling
c. Laboratory Investigations and Pre-Procedural Preparations
d. Venous Access Considerations in Children
e. Selection of Apheresis Equipment and Consumables
f. Blood Volume and Anticoagulation Adjustments for Pediatrics

a) Patient Assessment and Indication

- Comprehensive Medical History and Clinical Evaluation:

- Assess the underlying condition and determine whether apheresis is the appropriate treatment based on the patient's diagnosis (e.g., oncology, hematology, autoimmune disorders).
- Review previous treatments, response to therapies, and transfusion history, especially any history of alloimmunization or reactions to blood products.

- Assessment of Apheresis Indications:
  - Evaluate the specific indication for PBSC collection (e.g., hematopoietic stem cell transplantation) or therapeutic exchange (e.g., TPE or RCE). Clearly define the therapeutic goals (e.g., stem cell harvest, removal of abnormal cells or antibodies).
  - Therapeutic procedures can be guided by the category and grade of recommendations given in the relevant factsheets in the American Society for Apheresis (ASFA) guidelines. (2)

Table 1: Category recommendation for Apheresis according to ASFA, 2023. (2)

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as a second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision-making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB/Ethics Committee approval is desirable if apheresis treatment is undertaken in these circumstances.

Table 2: Grading of recommendations for apheresis according to ASFA, 2023(2)

Recomm-endation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
Grade 2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values

Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

For example, Acute exacerbation of myasthenia gravis is a Category I and Grade 1B recommendation for therapeutic plasma exchange to facilitate the removal of anti-acetylcholine receptor (AChR) antibodies.

b) Consent and Counselling

- Informed Consent: Comprehensive, age-appropriate counselling is offered to both the patient and their guardians. The procedure, its purpose, potential risks, and possible complications are clearly explained. Detailed information regarding the use of blood products, anticoagulation agents, and the required post-procedure monitoring is provided. Following the discussion, written informed consent is obtained from the patient (if they are an adult and able to comprehend) or the guardian (for children under 18, or if the patient's condition limits understanding).
- Psychosocial Counselling: Pediatric patients and their families may experience anxiety surrounding the procedure. Offer support and counselling, particularly in younger children, to alleviate fears.

c) Laboratory Investigations and Pre-Procedural Preparations

a. Complete Blood Count (CBC):

- Evaluate baseline blood counts to assess hemoglobin, platelet levels, and white blood cell count.
- Maintaining a stable hematocrit is crucial to ensure adequate oxygen delivery, especially in pediatric or anemic patients. When blood is drawn into the extracorporeal circuit, hematocrit levels may fall as red cells are temporarily removed from circulation. If the anticipated hematocrit falls below a safe threshold, it may be detrimental for the patient hence a red cell priming may be necessary. This is particularly relevant in smaller patients—such as those under 25 kg or with a total blood volume below 1000 mL—or in hemodynamically unstable individuals. A pre-procedure hematocrit of 21% is recommended while using Spectra Optia for apheresis; a value obtained below warrants pre-procedure circuit priming.
- A platelet count of 50,000/microL is prudent to have pre-procedure as the flow in the circuit causes a platelet loss of approximately 20-30,000 platelets.

b. Coagulation Profile:

- Assess coagulation parameters, particularly in therapeutic plasma exchange (TPE) and red cell exchange (RCE), to reduce the risk of bleeding complications during apheresis. Coagulation parameters – Prothrombin time, and activated partial thrombin time also serve as a guide for the selection of appropriate replacement fluid in case of therapeutic plasma exchange.
- The appropriate replacement fluid of choice in patients with deranged coagulation (eg liver disease) would be fresh frozen plasma. In patients with normal coagulation profiles (e.g. gulllian barre syndrome), a combination of normal saline and albumin may be used for TPE procedures with regular coagulation profile monitoring pre and post-procedures.

c. Crossmatch and Blood Typing:

- In patients undergoing RCE or TPE, ABO-Rh compatibility with donor blood products and minor crossmatching with replacement plasma is required in pediatric patients to account for low total blood volumes and diminished dilution effect of plasma components.
- In case of the requirement of red cells for priming the circuit the same should also be ABO-Rh matched and compatible with the donor/ patient. The red cell may also be required to be irradiated if the apheresis procedure is planned for a PBSC harvest.

d. Infectious Disease Screening:

- Perform necessary infectious disease screening of the donor/ patient according to criteria laid down in the Drugs and Cosmetics Act, particularly if donor cells or plasma will be used. In India, it is mandatory to screen for HIV, Hepatitis B&C, Malaria and syphilis if allogeneic products are to be transfused.
- Although a reactive result may not be an absolute contraindication to conduct the apheresis procedure since the procedure is therapeutic and may be life-saving in many indications.

d) Venous Access Considerations in Children

Body size and weight can dictate the length and French size of the dual-lumen central venous catheter. Rigid non-collapsable catheters are preferred as they can sustain the negative pressure exerted by the cell separator during the withdrawal or inlet of the machine.

a. Peripheral vs. Central Venous Access:

- Evaluate the need for peripheral or central venous access based on the patient's venous condition, anticipated volume of apheresis, and patient size. Usually, for allogenic procedures from healthy donors, peripheral access is

preferred as the introduction of central venous catheters itself can cause significant distress.

- Central venous catheters (CVCs) are often preferred in pediatric patients, as they allow for constant high flow rates required for efficient apheresis procedures.
- For single procedures (e.g. PBSC harvest from a well-mobilised matched sibling), bilateral peripheral access is preferred if peripheral venous calibre is adequate to accommodate an 18G/16G cannula. If multiple cycles of apheresis are needed (therapeutic plasma exchange) or difficult peripheral venous access, a CVC is more suitable.

b. Ultrasound-Guided Placement:
   - In younger children or those with difficult veins, ultrasound guidance may be employed to facilitate safe and effective central or peripheral venous catheter placement.

Table 3: Weight of child & catheter French for apheresis venous access (3)

Weight of Child (Kg)	Size of CVC (French)
<3	Consider two single lumen (5 Fr)
3-10	7 Fr, Double lumen
10-20	8/9 Fr, Double lumen
20-50	9/10 Fr, Double lumen
>50	11.5/12/13.5 Fr, Double lumen

The central catheters used should be large-bore, dual-lumen HD catheters as per the age of the child. The cannula should be able to accommodate the minimum blood flow rate of 20-40 ml/min. A peripheral line may be used in adolescents with a minimum size of 18G to draw and 22G for return.

e) Selection of Apheresis Equipment and Consumables

Extracorporeal volume can vary based on the type of device used and may even differ within the same device depending on the procedure. For instance, intermittent-flow instruments typically have a significantly higher ECV than continuous-flow instruments. Additionally, even within the same equipment, ECV can differ widely depending on the tubing sets used for each specific procedure. Given that the ECV will constitute a larger proportion of a child's TBV than an adult's, children are more susceptible to shifts in blood volume. Estimating the child's TBV is therefore necessary to anticipate the extent of this volume shift.

A. Apheresis Machines and Pediatric-Specific Considerations:

- Choose an apheresis machine that is optimized for pediatric use, with settings that accommodate smaller total blood volumes and allow precise control of blood flow rates.

Table 4: Extracorporeal volumes (ECV) of different apheresis equipment for various procedures. (4, 5)

Instrument	RBC Collection	Platelet Collection	Plasma Collection	Granulocyte collection	PBSC Collection
Alyx, Fresenius Kabi	110 ml	-	110 ml	-	-
Amicus, Fresenius Kabi	210/329* ml	210/329* ml	210/329* ml	-	163 ml
Aurora, Fresenius Kabi	-	-	200 ml	-	-

Autopheresis C, Fresenius Kabi	-	-	200 ml	-	-
MCS+ 8150, Haemonetic Corp	391-542 ml	-	391-542 ml	-	-
MCS+ 9000, Haemonetic Corp	-	359-480 ml	359-480 ml	359-480 ml	259 ml
PCS-2, Haemonetic Corp	-	-	359-480 ml	-	-
Trima Accel, Terumo BCT	190 ml	190 ml	190 ml	-	-
COM. TEC, Fresenius Kabi	-	-	-	120 ml	-
Spectra Optia, Terumo BCT	-	-	-	297 ml	MNC-191 ml CMNC - 297 ml

*Double Needle/Single Needle

B. Important Volume estimation for pediatric apheresis

The ECV may vary based on the equipment and the kit used. The following are the methods to calculate the various types of ECV:

a) Extracorporeal Volume (ECV) as a percentage of total blood volume
[Extracorporeal volume (ECV)/ Total Blood Volume] x 100= %ECV

b) Extracorporeal Red Cell Volume (ERCV) as a percentage of the total red cell volume
[Extracorporeal Red Cell Volume (ERCV)/ Red Cell Volume (RCV)] x 100= %ERCV

c) Intraprocedural Hematocrit
Initial Red Cell Volume (RCV)-ERCV/TBV] x 100= Intraprocedural Hematocrit (%)

Ensure the use of pediatric-appropriate tubing sets, blood filters, and other consumables to prevent excessive extracorporeal blood volume, reducing the risk of hypovolemia in small children.

C. **Need for RBC Priming**

The apheresis kit is primed with a compatible red cell unit to prevent the sudden hypoxic state due to the decline of the intravascular hematocirt. The need of Red cell priming is required in the following scenarios:

a. ECV > 15% of TBV
b. The weight of the patient is < 25 kg
c. Total blood volume is <1000 ml
d. Hemoglobin of less than 8 gm/dl
e. Low hematocrit levels (<20%) even if the ECV is <15% of TBV

Both red cells and plasma can be used for priming the apheresis kit however red cells are majorly used. The characteristics of the red cell used for the priming are the following:

a. Packed red blood cells
b. Compatible with the donor
c. Leukoreduced (preferred)

d. AHG crossmatched
e. Irradiated in case of a PBSC harvest
f. Hematocrit adjusted (some centres prefer matching of the HCT of the child to avoid an increase of HCT at the end of the procedure)

D. Blood Volume and Anticoagulation Adjustments for Pediatrics

- Calculation of Blood Volume:

  Accurately calculate the patient's total blood volume, as pediatric patients are particularly susceptible to volume shifts and hypovolemia. This is critical in setting apheresis parameters and adjusting anticoagulant doses.

i. **Nadler's formula:** It is a mathematical equation that estimates blood volume based on a patient's height and weight:
   - Men: Blood Volume = (0.3669 × H3) + (0.03219 × W) + 0.6041
   - Women: Blood Volume = (0.3561 × H3) + (0.03308 × W) + 0.1833
   - In the equations, H represents height in meters and W represents weight in kilograms.

ii. **Gilcher's Rule of 5:** Gilcher's Rule of 5 is used to estimate the safe volume of blood that can be collected from a donor (or patient) based on body weight. It provides an easy way to calculate the approximate blood volume that can be drawn without exceeding safety limits. According to this rule, for every 5 kilograms of body weight, 100 mL of blood can be safely removed. This rule is particularly useful in pediatrics, where careful attention to blood volume is critical due to the smaller total blood volume in children compared to adults.

Table 5: Gilcher's Rule of 5

	Obese	Thin	Normal	Muscular
Male	60 ml/kg	65 ml/kg	70 ml/kg	75 ml/kg
Female	55 ml/kg	60 ml/kg	65 ml/kg	70 ml/kg
Infant	80 ml/kg			
Child	70 ml/kg			

Blood volume estimation in children can be very challenging as there is no accurate method. The younger the child, the higher the total blood volume. The table below shows the estimated blood volume calculations however they may still vary depending on the disease and the overall status of the patient.

Table 6: Blood volume estimation in children

Blood volume estimation	**Age of the child**
85 ml/Kg	Normal sized newborn
80 ml/Kg	Toddler and Preschool Child
75-80 ml/Kg	Elementary school children
70-75 ml/Kg	Prepubertal children
70 ml/Kg	Adolescent

Anticoagulation:

Citrate is the preferred agent because of its regional effect, short half-life (30-60 min), and excellent safety profile. Citrate is infused in the circuit before the pump, where it chelates ionised calcium to prevent activation of the coagulation cascade.(6) Monitor calcium levels closely in patients receiving citrate anticoagulation to prevent hypocalcemia-related complications (e.g., tetany, cardiac arrhythmias). Weight-based dosing of anticoagulants, such as citrate or heparin, can ensure safe anticoagulation during the procedure.

Anticoagulant (AC) infusion rates of 0.8-1.2 ml/min/L of total blood volumes are usually optimum for pediatric patients. The citrate-related toxicity may be seen commonly due to an increased rate of citrate infusion or ACD-A infusion rate, increased blood flow rate, and decreased whole blood: AC ratio. Even the amount and type of AC in the replacement fluid can increase the risk of these toxicities. Longer procedures and procedures done on consecutive days also contribute to the increased risk.

Unlike most adults, young or critically ill children may be unable to communicate symptoms of hypocalcemia to the operator. Moreover, children may not display typical adult symptoms but instead show signs such as abdominal pain, vomiting, pallor, or hypotension. This makes it more challenging to monitor for citrate-induced ionized hypocalcemia in children through clinical observation alone.

The risk of citrate toxicity during therapeutic plasma exchange (TPE) is heightened with plasma replacement compared to albumin, especially in children with impaired citrate metabolism due to liver or kidney dysfunction. Plasma contains roughly four times the amount of citrate as albumin, resulting in a more significant increase in plasma citrate levels with plasma replacement (1.1 mM/L versus 0.2 mM/L with albumin).

While both plasma and albumin lower ionized calcium, plasma infusions reduce ionized calcium more than total calcium, whereas albumin decreases ionized and total calcium equally due to its direct

calcium-binding property. Only ionized calcium is physiologically active, so it should be monitored closely, particularly when plasma is the replacement fluid in TPE or when citrate anticoagulation is used for leukocyte apheresis.

If necessary, intravenous calcium supplementation should be administered to prevent serious hypocalcemia-related reactions. For pediatric apheresis, the AABB recommends considering a combination of heparin with citrate as an anticoagulation strategy unless contraindicated.

A retrospective study performed on 216 pediatric (<18 years of age) patients undergoing 1176 apheresis procedures for assessing the incidence of hypocalcemia and appropriate calcium supplementation was published in the Journal of Clinical apheresis in 2017. Patients on Prophylactic IV calcium replacement (2.16 mg/mL of elemental) at 1.4 times the inlet flow dramatically reduced the incidence of hypocalcemia and nearly eliminated symptomatic hypocalcemia. RCE procedures were associated with a low incidence of hypocalcemia. (7) Patients receiving FFP as replacement fluid did have a higher frequency of hypocalcemia, but this difference did not reach statistical significance. Though this study guides other pediatric centres for the safe and effective use of IV calcium replacement with regional citrate anticoagulation in apheresis therapies, prospective studies need to be conducted to substantiate these results.

Chapter 3:

Procedure phase

A. Setting Up the Apheresis Machine

- Machine Calibration:
    - Ensure that the apheresis machine is calibrated according to the pediatric patient's weight, total blood volume, and clinical condition. This includes setting appropriate blood flow rates, anticoagulation levels, and cycle times for the procedure (e.g., PBSC collection and therapeutic exchange).
    - Blood Flow Adjustments: Pediatric patients, especially infants, require lower blood flow rates than adults. The machine settings should reflect the child's size and physiological parameters to avoid complications such as hypovolemia.
- Pre-Procedure “Priming”:
    - The extracorporeal circuit should be primed with saline or an appropriate blood product (e.g., packed red cells) to minimize blood loss and prevent volume depletion during the procedure, especially in smaller children.
    - A major variable that differentiates pediatric from adult apheresis collections is the need for a blood prime in children weighing less than 25 kg. Weight less than 25 kg is the cut-off at which the patient's extracorporeal volume (ECV) during apheresis collection exceeds 10%-15% of the total blood volume (TBV). A blood prime is used because the ECV blood in a low-weight pediatric patient can be up to 50% of the patient's TBV during continuous apheresis collection. (8)
    - In pediatric peripheral blood stem cell (PBSC) collections, both autologous and allogeneic, using a red cell unit to prime the collection circuit is essential to prevent circuit clotting and optimize collection efficiency. The ideal red cell unit should be

crossmatch compatible with both the donor and the recipient to minimize any risk of transfusion reactions, especially if it's an allogeneic donation. Additionally, the unit should be irradiated and have a standardized volume, typically around 280 ml, to maximize the priming effect, ensuring the circuit is appropriately filled for optimal cell collection.

- In therapeutic apheresis procedures, irradiation of red cells is generally not required unless there's a specific indication, such as preventing transfusion-associated graft-versus-host disease (TA-GVHD) in immunocompromised patients.

B. **Monitoring During the Procedure**

- Continuous Monitoring:
  - Continuous monitoring of vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation) is crucial to detect early signs of hemodynamic instability, volume shifts, or adverse reactions.
  - Regularly monitor the child's hematocrit/hemoglobin levels and platelets (intra-procedure), as pediatric patients are more prone to volume depletion and anemia during prolonged apheresis procedures.
  - Calcium Monitoring:
    - Since citrate is commonly used as an anticoagulant in apheresis, monitor ionized calcium levels to prevent hypocalcemia, which can cause symptoms like paresthesia, tetany, or cardiac arrhythmias. Administer calcium supplements as needed.
- Venous Access Monitoring:
  - Regularly check the venous access site for patency, signs of leakage, or catheter malfunction. In central venous catheters, be vigilant for infection or thrombosis.

- Complication Monitoring:
    - Watch for complications specific to apheresis procedures, such as allergic reactions to blood products, hypovolemia, or citrate toxicity, which may present as muscle cramps, nausea, or tingling sensations.

C. **Managing Pediatric-Specific Complications**

- Hypovolemia:
    - Due to their smaller total blood volume, pediatric patients, especially infants, are at higher risk for hypovolemia. Pre-emptively adjust fluid replacement based on the child's weight and the expected extracorporeal volume.
- Hypocalcemia:
    - Pediatric patients undergoing apheresis procedures with citrate anticoagulation are more likely to experience hypocalcemia.
    - Monitor closely for clinical signs of hypocalcemia (e.g., muscle twitching, arrhythmias).
- Hypothermia
    - Small infants may be at the risk of hypothermia. In these procedures, an inline blood warmer should be considered. Hypothermia can also precipitate a sickle crisis in patients with sickle disease undergoing red cell exchange.
    - While using an inline blood warmer one should take care of the additional increase of ECV due to the addition of a blood warmer to the circuit.
- Allergic Reactions:
    - Pediatric patients may have allergic reactions to donor blood components used in therapeutic plasma exchange

which may be managed with antihistamines or corticosteroids.

- Signs and symptoms: Appearance of rashes, complaints of itching or a flushed face may be indicators of an allergic reaction. More severe reactions may present with difficulty breathing and a fall in saturation. Anaphylaxis, although rare, can be a complication in TPE procedures where plasma is used for replacement fluid with unknown IgA deficiency or plasma protein allergy.
- Antihistamines combined with dexamethasone if required, may be used for the treatment of acute reactions. No prophylactic antihistamine is required unless the patient has had a previous episode of allergy in similar settings.

D. Duration and Frequency of Apheresis Sessions

1. Procedure Duration:
    - The duration of the apheresis procedure depends on the type (e.g., PBSC collection vs. therapeutic plasma exchange) and the patient's clinical status. In general, pediatric procedures take longer due to lower blood flow rates and smaller extracorporeal volumes.
2. Frequency of Procedures:
    - The number of sessions varies by indication. For PBSC collection, multiple sessions may be required to achieve the target number of stem cells.
    - The target for CD34+ cell collection for a single autologous stem cell transplantation has generally been accepted to be 3 to $6x10^6$ CD34+ cells/kg. Also, a dose < $2x10^6$ CD34+ cells/kg can have a deleterious effect on engraftment. For allogenic collections, A CD34+ cell dose of 5 to $8x10^6$/kg is recommended. (9, 10)

- For therapeutic apheresis (e.g., TPE, RCE), the frequency is based on the patient's response to treatment and clinical need (e.g., daily TPE for autoimmune conditions or periodic RCE for sickle cell disease).
- The frequency and number of therapeutic plasma exchange (TPE) sessions depend on how quickly the pathogenic substance needs to be reduced for clinical improvement. Several factors influence TPE's effectiveness. One is the sieving coefficient, which measures how well a substance passes through a filter; a coefficient of 1 means it crosses easily, requiring fewer sessions, while a coefficient of 0 means it does not cross at all. The plasma half-life also matters; substances with shorter half-lives may be produced quickly, causing a faster rebound and requiring more frequent TPE sessions. Extravascular concentration affects removal speed, as substances spread outside blood vessels take longer to redistribute into the bloodstream for effective removal. Lastly, a high rate of synthesis of the substance may demand more frequent TPE sessions or additional therapies to slow its production. For IgG-related diseases, multiple TPE sessions reduce levels gradually due to IgG's long half-life and extravascular presence, while IgM can be quickly cleared with fewer sessions but rebounds faster.(11)

E. Rinseback

This is the process of pushing back the fluid in the kit at the end of the apheresis procedure. This is routinely done to make the euvolemic status at the end of the procedure. However, in pediatric apheresis after priming the patient is always in a euvolemic state. Hence doing a rinse back at the end may create a positive fluid balance in the patient. Rinse back results in positive fluid balance achieved as a bolus at the end of the procedure – +195-263mL in Spectra, less in newer devices.

Rinse back is usually avoided in procedures where priming is done using a red cell unit due to the risk of hypervolemia or increase of hematocrit. However, rinse back may be considered in cases where the patient is at risk of anemia.

F. Sedation

Sedation is not routinely offered to pediatric patients undergoing apheresis. Usually, distraction techniques such as watching TV, playing games, and activities distract children and parents in the room with the child. Sedation may be required in pediatric apheresis to ensure the patient remains calm and still during the procedure, which is critical for maintaining venous access and ensuring safety. The choice of sedation depends on the child's age, size, and the complexity of the procedure.

Some centres consider sedation in the following conditions:

- When the child is not able to lie still for the long duration of the procedure
- When the child is experiencing severe anxiety
- Development delay/ inability to cooperate with the procedure
- Very young age

Drugs considered for sedation are Ketamine, Midazolam and Dexmedetomidine (DEX). The dose and safety of the drugs are considered and consulted with the pediatrician based on the weight and other clinical conditions of the child. Some issues that need to be considered are the risk of aspiration and close monitoring of the oxygen saturation, heart rate and respiratory rate. The set-up should be well-equipped with the required resuscitation equipment.

Chapter 4:

Post-procedure phase

Apheresis, particularly in pediatric patients, requires careful attention post-procedure to ensure optimal recovery and to prevent potential complications. This chapter will cover post-procedure care, monitoring, and management of complications, and guide nutritional and hemodynamic support following pediatric apheresis.

1. Post-Procedure Care

The conclusion of an apheresis procedure marks the beginning of a crucial phase in the overall care of pediatric patients. Post-procedure care includes various steps to ensure patient stabilization and recovery while preventing adverse events. Although apheresis is a relatively safe procedure, it is not without potential complications. The risk of the rate of adverse events during apheresis is generally greater in therapeutic procedures and autologous stem cell collection procedures as compared to allogenic stem cell donor procedures. This is due to co-morbidities of patients in the therapeutic setting and autologous donation as opposed to healthy pediatric donors.

Apheresis staff must understand these complications and adverse events to try and prevent such incidents from occurring. The ability of the staff to detect or pre-empt adverse events and initiate prompt corrective action to minimise the impact on the patient/donor and/or procedure is essential. Many apheresis complications may develop as a result of the procedure itself or from the patient's primary or secondary medical conditions. Identifying any pre-existing medical conditions and determining the possible impact on the management of the patient during an apheresis procedure, aids in minimising or preventing any adverse events. Some of the key elements involved in post-procedure care:

A. Stabilization and Observation

Immediately after the procedure, the patient should be moved to a recovery area for close observation. Vital signs, including blood pressure, heart rate, respiratory rate, and temperature, should be monitored closely for at least an hour. During this period, the clinical team must look out for early signs of potential complications, including dizziness, fainting, or abnormal bleeding from venous access sites.

B. Addressing Fatigue

Fatigue is a common complaint after apheresis, particularly in pediatric patients due to the volume of blood processed relative to their smaller body size. Post-apheresis care should include rest and comfort, with attention to ensuring that the child does not overexert themselves in the immediate recovery period.

C. Fluid Balance and Hydration

Changes in intravascular volume occur as a result of fluid shifts during apheresis. In case of hypovolemia, ensuring adequate hydration is key in the recovery phase. If significant fluid shifts occurred during the procedure, intravenous fluids might be administered to maintain hemodynamic stability. Oral rehydration can also be encouraged, depending on the child's condition.
Fluid overload may also occur in some patients with cardiac/renal dysfunction. So close monitoring and management is required.

2. Post-Procedure Monitoring

Continuous monitoring is essential to detect and manage complications early. The following parameters should be routinely assessed:

A. Vital Signs and Hemodynamics

Monitoring heart rate, blood pressure, and oxygen saturation is critical to assess for hypovolemia or fluid overload. Sudden changes in these

parameters can indicate serious post-procedure issues like vasovagal reactions or hypovolemia, which require immediate intervention.

B. Blood Chemistry and Laboratory Tests

Laboratory tests, such as complete blood count (CBC), electrolyte panel, and coagulation profile, should be performed post-procedure to evaluate any significant deviations from baseline. This is particularly important in cases where large volumes of plasma or specific cellular components have been removed.

3. Managing Immediate Post-Apheresis Complications

Despite precautions, complications can occur following pediatric apheresis. Quick identification and management are essential to avoid further harm.

A. Hypovolemia

Hypovolemia due to excessive removal of blood components or inadequate fluid replacement during the procedure can manifest as low blood pressure, rapid pulse, dizziness, and fainting. Immediate treatment involves fluid replacement via IV access and monitoring the patient's response.

B. Electrolyte Imbalance

Electrolyte imbalances can arise, particularly in therapeutic procedures such as plasma exchange or red cell exchange apheresis where plasma or cellular components are removed or replaced. Hypocalcemia is a common concern in pediatric apheresis due to citrate anticoagulation. Symptoms include numbness, muscle cramps, and, in severe cases, cardiac arrhythmias. Administering calcium gluconate or calcium chloride either prophylactically during the procedure or reactively can correct this imbalance.

C. Complications related to Vascular access

The complications related to vascular access may be more frequent in apheresis procedures due to the longer indwelling time of the catheter.

The complications may include Haematoma, Venous sclerosis, Thrombosis, Infection, injury of Nerve, muscle or tendon.

Bleeding or hematoma formation at the venous access site is a relatively common occurrence, especially if the patient has received anticoagulants. Pressure must be applied to the venipuncture sites until hemostasis is achieved. If bleeding persists or worsens, further investigation and possibly imaging may be necessary to rule out vascular injury.

D. Coagulopathy

It is seen in a therapeutic setting. The altered coagulation status occurs post therapeutic plasma exchange when plasma is exchanged with replacement fluids, which do not have coagulation factors. So transfusion of Fresh frozen plasma may be considered.

E. Allergic Reactions and Infections

This is in the case of a therapeutic setting and is associated with blood products used as replacement fluid in plasma exchange, i.e. Albumin, plasma etc. Patients may experience allergic reactions which can range from mild hives and rashes to severe anaphylaxis. Immediate treatment includes antihistamines, corticosteroids, or epinephrine depending on the severity of the reaction. The venous catheter site should also be checked for signs of infection, including redness, swelling, or purulent discharge.

F. Pharmacological Changes

Especially witnessed in a therapeutic setting due to the removal of large quantities of plasma during plasma exchange. Plasma removal may decrease the concentration of certain medications. The quantity of medication removed is related to its plasma binding capacity, distribution and clearance of the drug. So the dose alteration of the drug may be required.

4. Nutritional and Hemodynamic Support

The body's response to apheresis, particularly in growing children, places an increased demand on nutritional and hemodynamic support to promote recovery.

A. Nutritional Support

A pediatric patient who has undergone apheresis may require adjustments to their nutritional intake to aid recovery and maintain normal physiological function. Special attention should be given to restoring protein, electrolytes, and other micronutrients lost during the procedure. However, the detailed diet advise should be in accordance with the underlying disease also.

Protein and Caloric Intake: Plasma exchange and other apheresis procedures can deplete protein levels. High-protein diets, including lean meats, legumes, and dairy products, should be encouraged post-procedure.

Electrolyte Replacement: Oral or intravenous electrolyte solutions may be necessary, especially for patients who experience significant shifts during the procedure.

Iron and Micronutrients: For children undergoing red cell exchange, ensuring adequate iron and vitamin levels, particularly vitamin C and B12, can support the regeneration of blood cells.

B. Hemodynamic Support

Post-apheresis care often requires careful management of fluid status to avoid hypovolemia or fluid overload. Key aspects include:

IV Fluid Administration: If there is evidence of dehydration or hypotension following the procedure, IV fluids may be necessary. Isotonic solutions are preferred for quick repletion without significant fluid shifts.

Blood Transfusions: In cases where blood components, such as red cells, are removed in significant amounts, transfusions may be required to prevent anemia or restore oxygen-carrying capacity.

Packed red blood cells (PRBCs) or other blood products can be administered based on post-procedure hematocrit levels. Mechanical Haemolysis may cause potential destruction of Red Blood Cells within machine circuitry as a result of collapsed or kinked tubing and improper harnessing of kit. So patient's urine needs to be monitored for the presence of hematuria.

4.3 Monitoring and Re-assessment

Following nutritional and hemodynamic interventions, regular reassessment of the patient's clinical status is necessary. Repeated CBC, electrolyte panels, and hemodynamic assessments should be performed, adjusting care as needed based on the patient's response.

Conclusion

Pediatric apheresis requires meticulous post-procedure care, given the physiological differences in children compared to adults. Stabilizing the child, monitoring for complications, and providing appropriate nutritional and hemodynamic support are critical for ensuring successful recovery. This comprehensive approach helps mitigate risks and promotes a smoother post-procedural experience for pediatric patients.

Chapter 5:

Special Considerations in Pediatric Apheresis

In pediatric care, apheresis encounters extra challenges because of the changing physiology and anatomy of developing children. Most of the research is based on studies in adults, and pediatric treatment is often informed by insights from adult medicine. Several unique factors distinguish pediatric apheresis from adult procedures, primarily related to the child's age, size, and developmental stage. To address these issues, we need to give special consideration and place particular focus on low-weight infants, as well as the ethical issues surrounding apheresis in pediatric populations. Providing family counselling is also essential in the care of these patients, ensuring that parents and guardians receive complete information and support throughout the entire process.

1. Apheresis in Low-Weight Infants

Apheresis in low-weight infants presents distinct challenges that require tailored approaches to ensure safety and efficacy. These challenges include their small blood volume, limited venous access, and increased risk of complications. Below are some key factors to consider when performing apheresis in low-weight infants:

a) Hemodynamic Stability

Determination of a precise pre-apheresis total blood volume may be difficult in many ill children because factors such as baseline health, pre-existing anemia or blood loss, and the current ongoing disease process may all alter what would otherwise be expected for total blood volume. In addition, Low-weight infants have a significantly smaller blood volume than older children and adults, making them more susceptible to hemodynamic instability during apheresis. Even slight changes in fluid balance can lead to hypotension, hypovolemia, or fluid overload. To prevent these issues following precautions may be undertaken:

- Compensation for extracorporeal Blood Volume:

  If the apheresis device settings could be modified to reduce the amount of blood outside the infant's body at any given moment, this challenge could be mitigated. However, current apheresis equipment is primarily designed for adults, making it difficult to precisely control flow rates in pediatric patients. To partially overcome this limitation, special measures, such as priming the system can be considered. While circuit Priming, it is essential to prime the circuit with a solution that supports intravascular stability. Red cell priming is recommended for smaller children or those who are acutely ill or anemic. This can be achieved using packed red blood cells diluted with saline or 5% albumin to reach a hematocrit level close to 40% or another clinically appropriate target. For larger or hemodynamically stable children, priming may also be done using 5% albumin or 0.9% saline.

- Close Monitoring of Vital Signs: Continuous monitoring of blood pressure, heart rate, and oxygen saturation is critical during the procedure. Fluid replacement, if needed, should be meticulously controlled to maintain stability.

2. Venous Access

Obtaining and maintaining venous access in low-weight infants is another significant challenge due to their smaller and more fragile veins. Specialised approaches include:

- Use of Central Venous Catheters: In many cases, peripheral venous access is inadequate for apheresis due to the inability to withstand the negative pressure generated by the machine inlet flows. Central venous catheters, such as peripherally inserted central catheters (PICC lines), are preferred as they allow for stable and continuous blood flow during the procedure. For urgent treatment in the pediatric intensive care unit or for projected prolonged apheresis therapy, standard pediatric hemodialysis catheters work well.

- Ultrasound-Guided Venous Access: Using ultrasound to guide catheter placement can increase the success rate of establishing venous access and reduce complications such as vessel injury.

3. Anticoagulation Management

Low-weight infants are at a higher risk of bleeding complications due to anticoagulation used during apheresis. Citrate is commonly used as an anticoagulant, but infants are particularly prone to citrate toxicity, which can lead to hypocalcemia, seizures, and cardiac arrhythmias. Another most common adverse sequelae of citrate anticoagulation is metabolic alkalosis. Citrate is metabolized by the liver into bicarbonate and some children with ongoing citrate exposure can produce a profound increase in serum bicarbonate levels and eventually a metabolic alkalosis that may complicate electrolyte balance and clinical care. This is less commonly seen during briefer exposures to citrate but can nonetheless complicate the course of some children on apheresis.

Key strategies for managing anticoagulation include:

- Frequent Monitoring of Calcium Levels: Calcium supplementation during the procedure is often necessary to prevent citrate-induced hypocalcemia. Monitoring ionized calcium levels throughout the procedure allows for timely adjustments.
- Adjusted Citrate Dosing: Lower citrate doses may be required for infants compared to older children and adults. The healthcare team must balance effective anticoagulation with minimizing the risk of citrate toxicity.

4. Blood Product Compatibility

Infants may require priming before apheresis & may also require infusion of plasma or red blood cell during plasma exchange & red cell exchange depending on their clinical condition. In these cases, it is important to ensure that any replacement products used during the procedure are ABO and Rh compatible to reduce the risk of hemolytic reactions. Additional considerations include:

- Irradiated Blood Products: In certain situations, such as for immunocompromised infants, or in case the donor is a prospective transplant patient, irradiated blood products may be required to prevent transfusion-associated graft-versus-host disease (TA-GVHD).
- Volume Management: Given the infant's limited blood volume, care must be taken to avoid both under and over-transfusion of blood products during and after the procedure.

5. Hypothermia

Pre-warming blood and replacement fluids may be considered in pediatric patients to make apheresis procedures unique and overcome the challenge of hypothermia in this group of patients. In calculating circuit volumes, any blood-warming equipment and tubing attached to the main apheresis circuit must also be considered because their volumes, especially in young children, are not inconsequential. For instance, blood warmer tubing by itself can contribute up to 40 mL of total extracorporeal volume.

6. Ethical Considerations in Pediatric Apheresis

Ethical issues are inherently complex in pediatric medicine, as decisions must balance the best interests of the child with respect for family values and autonomy. In pediatric apheresis, ethical dilemmas often arise when there is uncertainty about the risks and benefits of the procedure or when parents' decisions conflict with medical recommendations. Key ethical considerations include:

7. Informed Consent

Informed consent for pediatric apheresis is obtained from the child's parents or legal guardians. However, challenges arise when parents are faced with making decisions on behalf of their child for complex and potentially high-risk procedures. For informed consent to be ethically sound, healthcare providers must ensure that:

- Comprehensive Information Is Provided: Families must receive clear, detailed information about the procedure, including the potential risks, benefits, and alternatives. The information should be presented in a way that is understandable to those without medical training.
- Parental Concerns Are Addressed: Parents often have significant emotional responses to medical procedures in their children. It is important to acknowledge their concerns, provide empathetic support, and engage in a shared decision-making process.
- Consideration of Assent: For older children who can understand the situation, obtaining their assent, alongside parental consent, is important. This respects the child's developing autonomy and allows them to be active participants in their own healthcare.

8. Best Interests of the Child

In all cases, medical decisions should be guided by what is in the best interest of the child. However, determining the best interest may be complex when balancing the potential benefits of apheresis against its risks. In some cases, ethical dilemmas arise when:

- Parental Refusal: Parents may refuse apheresis, especially if they have concerns about the procedure's invasiveness or risks. In life-threatening situations, refusal may necessitate legal intervention if the medical team believes the procedure is essential to the child's survival or well-being.
- Experimental or Novel Therapies: Some apheresis treatments may still be considered experimental in pediatric populations, especially for rare conditions. Families should be informed of the uncertainties and potential risks involved in novel or less-established therapies.

9. Family Counselling and Support

Family counselling is an integral part of pediatric apheresis, as parents and caregivers play a central role in decision-making, caregiving, and emotional support. Providing thorough counselling ensures that

families are prepared for the procedure and its aftermath. The psychological issues are something to remember for caregivers to keep children calm in their beds during procedures.

- Pre-Procedure Counseling: Before the procedure, the healthcare team should engage with the family to discuss the following:
    - Purpose and Goals of Apheresis: It is important for families to understand why apheresis is recommended and how it fits into the overall treatment plan.
    - Expectations for the Procedure: Families should be informed about what to expect during the procedure, including its duration, potential discomfort, and the role of any necessary medications.
    - Risks and Benefits: A balanced discussion of the risks and benefits is critical for families to make informed decisions. This includes an honest appraisal of potential complications and their likelihood.

- Emotional and Psychological Support
  The apheresis process can be stressful for both the child and their family. Emotional support should be available before, during, and after the procedure:
    - Pediatric Psychosocial Support: Child life specialists, counsellors, or psychologists can help children and their families cope with the stress of apheresis. These professionals use techniques like play therapy, relaxation exercises, and emotional counselling to ease anxiety.
    - Peer Support Groups: Families may benefit from connecting with other parents who have been through similar experiences. Peer support groups, either in-person or online, can offer practical advice and emotional encouragement.

- Post-Procedure Counseling and Follow-Up: After the apheresis procedure, families should receive guidance on the following:

- Signs of Complications: Families should be educated on potential post-procedure complications, such as infection at the catheter site, bleeding, or signs of hypocalcemia, and be advised on when to seek medical help.
- Long-Term Management: Depending on the child's underlying condition, apheresis may need to be repeated. The healthcare team should outline what future care and monitoring will entail.

Conclusion

Pediatric apheresis requires special considerations, particularly in low-weight infants, where hemodynamic stability, venous access, and anticoagulation must be carefully managed. Ethical challenges often arise in pediatric care, and it is critical to balance the child's best interests with parental decision-making. Comprehensive family counselling, both before and after the procedure, ensures that parents and caregivers are well-informed and supported, leading to better outcomes for pediatric patients undergoing apheresis.

Suggested reading and references:

1. Okafor C, Ward DM, Mokrzycki MH, Weinstein R, Clark P, Balogun RA. Introduction and overview of therapeutic apheresis. J Clin Apher. 2010;25(5):240-9.
2. Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.
3. Raina R, Joshi H, Chakraborty R, Sethi SK. Challenges of long-term vascular access in pediatric hemodialysis: Recommendations for practitioners. Hemodial Int. 2021;25(1):3-11.
4. Daniel D Summerfield EAB. Donor Apheresis Separators and their development. Apheresis: Principles and Practice, 4th ed, Volume 2:Collection of blood components by Apheresis. 4, editor2021.
5. Abutalib S.A. PA, Pham H.P., Worel N. Best Practices of Apheresis in Hematopoietic Cell Transplantation: Cham, Switzerland; 2020.
6. Counts CS, American Nephrology Nurses' Association. Core curriculum for nephrology nursing. 5th ed. Pitman, N.J.: American Nephrology Nurses' Association; 2008. xiii, 1099 p. p.
7. Sigler K, Lee J, Srivaths P. Regional citrate anticoagulation with calcium replacement in pediatric apheresis. J Clin Apher. 2018;33(3):274-7.
8. Rahim MQ, Goebel WS, Delph J, Soundar E. Primed for change: The effect of a blood prime on peripheral blood stem cell collection and accuracy of a prediction tool in pediatric patients. J Clin Apher. 2023;38(5):540-7.
9. Arora S, Majhail NS, Liu H. Hematopoietic Progenitor Cell Mobilization for Autologous Stem Cell Transplantation in Multiple Myeloma in Contemporary Era. Clin Lymphoma Myeloma Leuk. 2019;19(4):200-5.
10. Prisciandaro M, Santinelli E, Tomarchio V, Tafuri MA, Bonchi C, Palazzo G, et al. Stem Cells Collection and Mobilization in Adult Autologous/Allogeneic Transplantation: Critical Points and Future Challenges. Cells. 2024;13(7).
11. Cervantes CE, Bloch EM, Sperati CJ. Therapeutic Plasma Exchange: Core Curriculum 2023. Am J Kidney Dis. 2023;81(4):475-92.

"As long as adequate venous access can be established, children should not be denied therapeutic apheresis because they are too small, too sick or, too anemic."

Dr Haewon Kim
Children's Hospital of Philadelphia, USA


POSTGRADUATE INSTITUTE OF CHILD HEALTH
SECTOR-30, NOIDA
बाल चिकित्सा एवं स्नातकोत्तर
शैक्षणिक संस्थान