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BLOOD LOSS AND FLUID REPLACEMENT IN PEDIATRIC PATIENTS

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Abstract

While strategies for the management of hemorrhage, transfusion and blood loss replacement in adults are well established, there aren't any concrete, evidence-based recommendations for pediatrics.

Promoting hemodynamic stability, preserving organ perfusion, minimizing transfusion-related injury, avoiding over-transfusion, and avoiding the deadly triad of coagulopathy, acidosis, and hypothermia are among the objectives of bleeding therapy in pediatric patients. At the beginning of treatment, crystalloid or colloid solutions may be used until blood products are available. Preventing dilutional coagulopathy requires caution. Monitoring end-organ perfusion and maintaining a healthy blood pressure are essential. Red blood cell transfusion should be matched with "yellow" blood product transfusion in the form of a 1:1:1:1 volume ratio of PBRC: fresh frozen plasma (FFP): cryoprecipitate: platelets form, in order to prevent coagulopathy and preserve sufficient oxygen supply to tissues.

Hemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and transfusion-related immunomodulation (TRIM) are only few of the hazards connected with blood transfusion.

Rapid and appropriate access for blood product transfusions is essential. To calculate the maximum permitted blood loss, a weight-based estimated blood volume (EBV) is used. A tried-and-true strategy for managing intraoperative hemorrhage should be used, including blood preservation techniques, balanced transfusion ratios and adjunct medicines. Transfusion decisions may be influenced by point-of-care and laboratory tests, such as thromboelastography.

Transfusion-related laboratory abnormalities should be watched for and treated as appropriate. Children's platelet transfusion thresholds are unclear; however, maintaining a platelet count of 50,000/L while bleeding continues is seen as sufficient in adults. When EBV loss surpasses 50%, fresh frozen plasma (FFP) and platelet transfusions should be taken into consideration. Electrolyte levels, particularly those of calcium, magnesium and potassium, need to be monitored.

As a result, controlling severe bleeding and transfusion in pediatric patients necessitates specialized approaches, such as meticulous preoperative planning, goal-directed therapy and

monitoring of laboratory derangements. PBM program implementation can improve patients' outcomes and lower transfusion-related hazards.

Key Words*: blood loss, fluid replacement, pediatric patients.*

Introduction

A multimodal and multidisciplinary strategy is necessary for the control of bleeding and fluid replacement in pediatric patients. Interventions start before surgery to identify patients who might have a higher risk of bleeding. This may involve identifying any underlying coagulation disorders (inherited or acquired), stopping the use of specific antithrombotic drugs, or identifying and treating anemia before undergoing any major surgical procedures. The proper use of blood products is receiving increased focus, and recommendations are shifting to a more evidence-based individualized approach (1-4).

It is crucial to stay up to date on the most recent research in this dynamic area of medicine where there are numerous treatment choices available along with surgical procedures of varying complexity. However, there is comparatively little high-quality research in pediatric patients to support evidence-based guidelines when compared to adult practice. This document updates recommendations, suggestions and assertions from a comprehensive literature search to address the whole spectrum of treatment and retains clinical practice recommendations from the existing guidelines (1-6).

Material and Methods:

The key words "pediatric patients," "blood loss "and" fluid replacement" were used in the key word searches strategies of the Medline, IBSS databases, Pubmed, CINAHL, and reference lists of the primary articles that were found during the initial search. To make this method robust and sensitive enough to cover all of the requested keywords, further searches were conducted. Personal and college libraries were also searched for texts on the topic. Guidelines, case reports, editorials and commentaries were included in the search result as well.

Fluid Replacement

The introduction of intravenous (IV) fluids is necessary for children having surgery to address the fluid need resulting from perioperative deficiencies (fasting, hemorrhage and third space losses; gastrointestinal, renal, or cutaneous losses). In a typical person with normal intracellular fluid (ICF) and extracellular fluid (ECF) volumes for a 24-hours period, maintenance therapy represents the fluids and electrolyte requirements due to predicted physiological losses from breathing, sweating and urine output. In order to counteract the effects of anesthetics, proper tissue perfusion must also be maintained, which requires fluid (7). In order to maintain or restore the child's normal physiological condition, including normovolemia, normal tissue perfusion, and normal metabolic activity, normal electrolytes, and normal acid-base balance, intraoperative fluid administration is required (8). There has been a lot of studies done on perioperative fluid administration, specifically on the type of fluid supplied (crystalloids or colloids) and the composition (isotonic vs. hypotonic) (9). Children who have had trauma or major surgery may experience intraoperative blood loss.The most frequent cause of cardiac arrest in children under

anesthesia is hypovolemia brought on by blood loss (10). The major objectives of intraoperative management of a bleeding child are to prevent hypotension, maintain appropriate tissue perfusion and oxygenation, and maintain hemostasis. On the other hand, autologous blood transfusions and their constituent parts are linked to higher rates of morbidity and mortality, due to transfusion-associated circulatory overload (TACO) and transfusion-associated acute lung injury (TRALI) (6,11).

Guidelines for Perioperative Pediatric Fluid Therapy

Guidelines by various societies (APA), NICE and guidelines from Association of the Scientific Medical Societies of Germany have been proposed for calculating the volume of fluid to be administered during surgery (8,12-14).
The recommendations state that, in order to minimize patient's discomfort, dehydration and ketoacidosis, preoperative fasting periods for children should be as brief as feasible. Based on the liberalization of fasting guidelines for pediatric patients, which now allow clear fluids for up to 1–2 hours, the amount of IV fluids required to be covered for preoperative fluid deficit may be decreased. However, despite the 2-hours recommendation for fasting, there are several circumstances where a child may be fasting for more than 6 hours (14).

Fluid Maintenance Therapy and itsPhases

The Holliday and Segar 4-2-1 formula is used to calculate the maintenance fluid requirements (15), Table 1. The maintenance fluid administration of isotonic fluids based on the Holliday and Segar formula is advised by both APA (12) and NICE (13) guidelines. However, according to NICE guidelines, fluid intake should be limited by 50–80% due to the danger of water retention caused by non–osmotic ADH secretion (13). The German recommendations include starting with an initial infusion of balanced electrolyte solution containing 1-2.5% dextrose at a rate of 10ml/kg/h and then adjusting the rate as needed (8).

Table 1. The Holliday and Segar formula.

Weight (kg)	Hourly	Weekly
< 10kg	4ml/kg/h	100ml/kg/day
10 – 20kg	40ml + 2ml/kg for every kg>10kg	1000ml + 50ml/kg/day for every kg>10
<20kg	60ml + 1ml/kg for every kg>20kg	1500ml + 20ml/kg/day for every kg>20

There are four specific physiology-driven time periods for children that require IV fluids. The phase of resuscitation is when the IV fluids are required during the acute presentation window, in order to restore appropriate tissue perfusion, and stop or lessen end-organ damage. It is crucial to assess intravascular repletion and the trajectory of fluid gains vs losses in critically ill children throughout the titration phase, which occurs when IV fluids are switched from boluses to maintenance. A precise homeostatic balance between needs and losses should be achieved during the maintenance phase, which takes into account the fluids given during the first two stabilization periods. The convalescent phase, which follows the cessation of exogenous fluid delivery and the patient's return to intrinsic fluid management, is the last stage. A fixed

protocoled dose cannot be applied to all patients, and the fluid dose during these four phases of fluid treatment must be modified based on the individual physiological requirements of each patient (1,8,12-14).

Replacement Fluid Therapy

The APA guidelines state that blood or isotonic solutions and colloids, depending on the child's hematocrit, should be used to replace intraoperative losses (12).

It is difficult to quantify the third space loss, but it is generally estimated to be:

- 2ml/kg/h for superficial surgery minimal trauma,
- 4–7ml/kg/h for moderate trauma, and
- 5–10ml/kg/h for severe trauma surgery.

The rate of fluid delivery is not included in the NICE guidelines; only replacement of ongoing losses with isotonic saline is (13). Sumplemann et al. advise giving repeat dosage infusions of 10–20ml/kg of balanced, isotonic electrolyte solutions without glucose to patients with circulatory instability until the desired effect is attained (8). A necessary condition for proper venous return, cardiac output and sufficient tissue perfusion is a normal blood volume. Interstitial fluid moves toward intravascular space as blood volume falls. Stabilizing the circulatory system by infusing a balanced salt solution to maintain extracellular fluid volume and blood volume is the first step (14).

Colloids such albumin, gelatin and hydroxyethyl starches, are used as repeat dose infusions if the volume of crystalloids is too high in order to prevent interstitial fluid excess, which can cause hemodilution and a reduction in the oxygen supply. The entire dose, however, should not be more than 10 to 20ml per kilogram (not to exceed a 50ml/kg dose) (12-14).

Which Type of Isotonic Solution is Preferred?

A variety of IV fluids are commercially available for use on newborns and kids. The main differences between these solutions are the kind of electrolyte composition, the addition of a buffer, and whether or not they contain glucose.

There are many other kinds of isotonic solutions that can be administered, but the most popular ones are normal saline (NS), Ringer lactate (RL) and PlasmalyteTM (acetate). RL has a somewhat hypotonic osmolality of 273mOsmol/kg compared to normal saline's 286mOsmol/kg. These solutions contain a very high concentration of chlorine (156mmol/L) and administering significant amounts of them can lead to chloride overload, which can restrict renal blood flow and the renin-angiotensin-aldosterone system, resulting in hyperchloremic acidosis (16). Additionally, lactate can still be used for diagnosis as a marker of tissue perfusion because acetate, which is present in the solutions, is quickly metabolized by the liver in comparison to lactate. For intraoperative infusion, balanced electrolyte solutions are advised (17,18).The key action statements of APAare that isotonic solutions with suitable potassium chloride (KCl) and dextrose should be administered to patients aged 28 days to 18 years who need maintenance IVFs because they greatly lower the risk of hyponatremia (1A level ofevidence) (1,12).

Table 2. Composition of commonly used maintenance intra venous fluids (1).

Fluid	Glucose g/dL	Sodium	Chloride	Potassium mEq/L	Calcium	Magnesium	Buffer	Osmolarity mOsm/L
Human plasma	0.07 - 0.11	135-145	95-105	3.5-5.3	4.4-5.2	1.6-2.4	23-30 bicarbonate	308
Hypotonic solution								
0.25%NaCl	5	34	34	0	0	0	0	78
0.45%NaCl	5	77	77	0	0	0	0	154
Isotonic solution								
0.9%NaCl	5	154	154	0	0	0	0	308
Lactated Ringer	5	130	109	4	3	0	28 lactate	273
PlasmaLyte	0	140	98	5	0	3	27 acetate and 23 gluconate	294

Role of Colloids

There is significant debate over, and little research on the use of colloids intra operatively in pediatric patients (19,20). The majority research investigations that have demonstrated renal failure in sepsis patients, were conducted on adult patients. However, using moderate and high dosages of HES 130 has not been associated with renal failure in pediatric animal trials or in children having major heart surgery. When given to children during the perioperative period, intravascular volume expansion with low molecular weight 6% HES, did not seem to affect renal function, blood loss, or transfusion, according to a meta-analysis (21).

To evaluate their impact on children, the authors advised conducting high-quality RCTs due to the poor quality of the evidence.

Blood Loss and Need for Transfusion

Through research and practical experience in specific circumstances, the treatment of major bleeding and massive transfusion has been described in adults. Tourniquet use, damage control resuscitation techniques, balanced transfusion ratios and anti-fibrinolytic medication have all been demonstrated to have significant effects on reducing trauma-related death (22). There are number of regimens for managing large hemorrhage in children, many of which have been derived from the trauma literature and procedures for adults (23). Children are not miniature people (24).Pediatric strategies should focus on preventing the well-described lethal triad (coagulopathy, acidosis and hypothermia) associated with massive transfusion, as well as patients' or procedural risk factor awareness, system and provider readiness for potential hemorrhage in high-risk situations and intraoperative goal-directed care. During the perioperative phase, blood transfusions are frequently necessary, especially when children are having surgery, but it is particularly common during trauma, liver transplant, cardiac surgery, major spinal surgery, cranial vault surgery, neurosurgical procedures (arteriovenous malformations, Vein of Galen), and minimally invasive procedures where direct bleeding control can be challenging. Inherited bleeding disorders and other patient-related factors can potentially increase the chance of hemorrhaging (24). Assessment of the necessity for and value of blood

transfusion is thus a crucial component of anesthesia management. It's also crucial to realize that giving blood to kids entails serious risks for morbidity and mortality due to acute lung injury from transfusions, circulatory overload and hemolytic transfusion responses (25). These have led to the implementation of patients' blood management (PBM) programs, which offer evidence-based treatment and enhance outcomes by using the best possible transfusion therapy. Although these programs have been used successfully in the adult population, they have not yet gained much attraction with newborns, young children and babies (11,26). For neonates, babies, and children as well as adults, many practice guidelines and recommendations for perioperative blood management have been published (27,28,29). Patients' blood management (PBM) is the timely implementation of scientifically supported medical and surgical principles intended to preserve hemoglobin concentration, maximize hemostasis, and reduce blood loss in order to enhance patients' outcomes (5). The establishment of a multidisciplinary PBM program inside a facility can assist in addressing the system demands and strain brought on by a patient suffering from a major hemorrhage in a way that is both effective and safe. This program should specify the protocols to be followed, the transfusion triggers to be used to start a large-scale transfusion event, and the quantity/ratio of blood products delivered throughout the event. This lessens needless transfusions, while enabling safe and effective optimization of blood product consumption. The patient's morbidity and mortality may go down, and the institution's medical expenses might go down consequently (8). According to the PBM programs, infants and children may require stringent hemoglobin thresholds (the objective is 7g/dL for patients who are hemodynamically stable). A restrictive Hb trigger (7.0g/dL) was shown to be equally safe and efficacious as a liberal Hb trigger (9.5g/dL) in a randomized controlled trial of stable critically sick children (33). This has not been generalized to unstable individuals, and children with cardiorespiratory impairment and/or anemia symptoms may require a higher threshold. If necessary, red blood cell transfusions should be single donor, irradiated, fresh and leucocyte depleted.

The requirement of blood transfusion depends on many factors like age, quantity of blood loss, the baseline hemoglobin concentration and different blood physiology. Neonates and infants have higher blood volume per weight (Table 2) but are less tolerant of the loss. In addition, the metabolic rate and baseline oxygen demands are greater than in adults. Preoperative iron deficiency anemia is more prevalent in this population and increases the risk of blood transfusion requirement intra operatively. Neonatal hemoglobin (Hb) is more than 70% fetal Hb in term neonates compared to 90% in preterm implying decreased oxygen delivery to the tissues (14).

Table 3. Normal blood volume in neonates and children.

Age	Blood volume
Preterm neonate	90 - 100ml/kg
Full term neonate - 3 months	80 – 90ml/kg
Above 3 months	70 – 80ml/kg
Above 2 years	70ml/kg

To minimize swelling, edema and hemodilution in a bleeding child, the intraoperative goal should be to maintain normovolemia while avoiding hypervolemia. Initial fluid replacement for blood loss can be accomplished by giving crystalloids or colloids in a 2:1 ratio to the predicted blood loss. The preferable fluids are Ringers Lactate (273mOsm) and Plasmalyte (294mOsm), which are associated with less severe acidosis than isotonic saline. It may be necessary to provide colloids in a 1:1 ratio in the event of fast blood loss and hemodynamic instability (2,14).

The maximum permitted blood loss (MABL), which is determined by following formula determines when to give children blood:

MABL= EBV (H0 - H1)/H0

(EBV = estimated blood volume; H0 = starting Hct; H1 = lowest acceptable Hct).

Age, Hb level and concomitant illness states, determine whether blood transfusions are necessary (30).

On the other hand, massive hemorrhage in children is defined as blood loss that exceeds one circulating blood volume (CBV) in a 24-hours period, blood loss that equals 50% of CBV in a 3-hours period, or transfusion at a rate of 10% of total blood volume (TBV) every 10 minutes (5). According to this definition, the healthcare professional must figure out the patient's weight-based estimated circulation blood volume (EBV) Table 2.

Less is known about massive transfusion. Warfare literature offers one potential definition. Greater than 40ml/kg of blood transfused within the first 24 hours after an accident in a pediatric patient is regarded as a major transfusion and is linked to a higher risk of in-hospital death (31,32).

Goal-directed therapy in management of hemorrhage aims to:

1. Promote hemodynamic stability as indicated by vital signs,

2. To ensure oxygen supply and end organ perfusion,

3. To lessen the negative effects and risks of transfusion,

4. To prevent over-transfusion by using laboratory and point-of-care diagnostics, as well as the appropriate usage of blood components,

5. To avoid the fatal triple threat of hypothermia, acidosis and coagulopathy.

However, initial therapy may need boluses of crystalloid or colloid solutions until blood products are available. Care must be taken since excessive amounts may cause dilutional coagulopathy. Temporizing measures, such as vasopressor support, may be necessary to maintain a healthy blood pressure after a major bleeding (5,24,32). Appropriate blood pressure targets differ by age and tend to rise as people get older. In preterm infants and teenagers, it is advised to keep mean systolic blood pressure (SBP) at an average of 55 mm Hg and 110 mm Hg, respectively (31). Monitoring end organ perfusion can be done with the aid of lactate, base deficit monitoring, and

urine output. Non-invasive monitoring of cerebral oxygenation using near infrared spectroscopy (NIRS) has also been linked to increases in brain tissue oxygen tension (24).

Red blood cell transfusion should be balanced with "yellow" blood product transfusion in the form of a 1:1:1:1 volume ratio of PBRC: fresh frozen plasma (FFP): platelets: cryoprecipitate to prevent coagulopathy and maintain adequate oxygen delivery to tissues when massive hemorrhage necessitates massive transfusion. When EBV loss exceeds 50% of total blood volume, transfusion of fresh frozen plasma (FFP), platelets, and cryoprecipitate should be taken into consideration. If possible, laboratory testing such as thromboelastography (TEG or ROTEM) and point-of-care tests such as thromboelastography should be used to guide and direct the delivery of blood products (1,2,5,24,34).

On the other hand United Kingdom Transfusion service recommend red cell:FFP transfusion ratios to be based on volume (mL) rather than "units" when used. After the patient has been stabilized with "damage control resuscitation" and transfusions based on clinical indicators, the proper treatment aims (based on speedy return laboratory or near-patient Hb 80 g/L, fibrinogen > 1.0 g/L, PT ratio 1.5, and platelet count > 75 109/L are the results of testing.

When managing a hemorrhage, a number of risk factors and adverse effects should be taken into account. In addition to non-hemolytic events including transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and transfusion related immunomodulation (TRIM), transfusion of blood products can result in hemolytic transfusion reactions.

Additionally, banked blood products can result in citrate toxicity and aberrant electrolyte levels such hyper- and hypokalemia, hypocalcemia, and hypomagnesemia (5,24). It is advised that blood cleaning or the use of "fresh" red blood cells obtained within 7 days of transfusion lower the risk of hyperkalemia in children under 1 year old or 10 kilos (5). Due to dilution, red cell lysis, and blood preservation components, blood transfusion causes lab derangements. If available, electrolyte and coagulation testing should be used to look for anomalies. If testing is not possible, however, some anomalies (such as acidosis and hypocalcemia) may be treated empirically. Calcium can be replaced with calcium gluconate (30-100 mg/kg) or calcium chloride (20 mg/kg) (5), and sodium bicarbonate (1 mEq/kg) can help with acidosis (31). Calcium chloride, if there is line infiltration, might result in tissue necrosis. It should only be managed through centralized access. A safer drug for peripheral delivery is calcium gluconate. Children's minimal platelet count transfusion thresholds have not been established, although in the adult population, a platelet count of $50x10^9$ platelets/L is now regarded as sufficient with persistent bleeding (5). The platelet count will rise by $50\text{-}100x10^9$ platelets/L following a transfusion of 5–10 ml/kg of platelets. The pediatric population has also noticed this. For transfusion, FFP should be administered at a dose of 10-15 ml/kg. This can support fibrinogen levels, which can affect coagulation when they are between 150 and 200 mg/dL (24). It's important to keep fibrinogen levels stable. To maximize hemostasis during heavy transfusion, maintain fibrinogen > 150 mg/dL. The best sources of fibrinogen are cryoprecipitate and fibrinogen concentrate (5).

Autologous blood can be drawn from the operating room using cell salvage procedures for processing and transfusion. It might be challenging to gather sufficient numbers of salvageable cells from babies for transfusion. Overall, patients >10 kg and with >40% bood loss may benefit from cell salvage the mos. The use of cell salvage during tumor surgery or in situations where blood cell lysis occurs is debatable. It is also acknowledged that in many places, this management approach might not be appropriate (5).

Both adults and children have been investigated on the adjunctive use of antifibrinolytic treatment to reduce surgical bleeding (2,35). One of the most widely used antifibrinolytics is tranexamic acid (TXA). According to the PED-TRAX trial, TXA is linked to lower mortality in children who have been injured and that "the timely administration of TXA to injured patients is associated with a survival advantage and this advantage seems to extend to the injured pediatric population" (36). A loading dose of 10 to 30 mg/kg (maximum 2 grams) administered over 15 minutes, followed by an infusion of 5 to 10 mg/kg/h, is the optimal TXA therapeutic dosage range (24,37). These dosages have been demonstrated to increase effect while minimizing negative side effects, such as seizures. TXA has been used safely in pediatrics, although it should not be administered to kids who have consumption coagulopathy or active thromboembolic illness. Patients with acquired thrombotic disease and renal impairment are generally contraindicated (37). Patients with genetic or acquired platelet function problems may benefit from pharmacological treatment with an anti-fibrinolytic, DDAVP, or rFVIIa.

Indication for Red Blood Cell transfusion for the critically ill child Table 3. (1,2,4,28-30,38).

- If the Hb concentration is less than 5 g/dL in children who are critically ill or who are at risk for critical illness, an RBC transfusion is advised (1C recommendation).
- We cannot propose a specific RBC transfusion decision-making method for critically sick children or those at risk for critical illness upon physiologic metrics and biomarkers.
- We advise against giving RBC transfusions to children who are critically ill or who are at risk for critical illness, who are hemodynamically stable and have a Hb concentration > 7 g/dL (1B recommendations).
- There is inadequate evidence to make a recommendation about transfusion thresholds for critically ill children with an Hb concentration between 5 and 7 g/dL, according to a weak recommendation, low quality pediatric evidence (2C).
- If the child is with respiratory failure. It is not advisable to give transfusion if Hb is <5 g/dL and not to give if it is >7 g/dL. However, it is reasonable to consider transfusion based on clinical condition when Hb is between 5 – 7 g /dL.
- When in shock or septic shock it is not recommended to administer RBC if Hb is > 7 g/dL.
- Exception is child with brain injury. They should have transfusion if Hb falls between 7 – 10 g/dL.

Table 4. Summary of BCSH recommendations for neonatal transfusion

Postnatal age	**Suggested transfusion threshold of Hb g/dL**		
	Mechanically ventilated	On oxygen/CPAP	No oxygen

First 24h	<120	<120	<100
Week 1	<120	<100	<100
Week 2	<100	<95	<75-85
Week 3	<100	<85	<75-85

European Society of Anesthesia recommends following triggers for intraoperative transfusions and volume control during active bleeding:

- Maintaining a target hemoglobin concentration of 7 to 9 g/dL (1B)
- To give an individualized strategy to identifying individuals who may benefit from transfusion, advise central venous oxygen saturation or arterial-venous oxygen difference surrogates for the oxygen delivery to consumption ratio in patients who have a superior vena cava catheter in place (1C).
- Recommend repeated measurements of a combination of tissue perfusion, tissue oxygenation, and the dynamics of blood loss during acute bleeding using haematocrit/haemoglobin, serum lactate, and base deficit (1C).
- Extending these analyses by measuring cardiac output, dynamic variables of volume status (stroke volume variation and pulse pressure change), CO_2 gap, central venous oxygen saturation, or any combination of these (1C).
- Replacing extracellular fluid losses with isotonic crystalloids as soon as possible and according to a set protocol (1B).
- Compared to crystalloids, iso-oncotic colloids require less volume to accomplish macro- and micro-haemodynamic stabilization and induce less tissue edema(C).
- Colloids can worsen dilutional coagulopathy in patients with severe bleeding by having extra effects on fibrin polymerization and platelet aggregation(C).
- For crystalloids and as a foundational solute for iso-oncotic preparations, we advise the use of balanced solutions(2C).
- In order to aid transfusion in neonates and kids having cardiac and noncardiac surgery, viscoelastic hemostatic assay (VHA) guided therapies is recommended (2C).

In a recent RCT, an individualised strategy based on a central venous oxygen saturation threshold of 70% allowed for a more restrictive RBC transfusion strategy with no incidence on postoperative morbidity or 6-month mortality (2). Furthermore, a retrospective study in critically ill patients found that when A–V O_2 difference is greater than 3.7 ml, it could provide a more personalized approach in identifying patients who might benefit from transfusion, as indicated by lower mortality compared with those who received transfusion when A–V O_2 diff was lower.

Indication for platelet transfusion

Indication for platelet transfusion are differing depending of pediatric patient's age and the typical platelet dose is 5–10 mL/kg, as tolerated.

Patients < 4 month of age

- Infants with low platelet production or platelet count of 20–30,000/μL (20–30 x 109/L);

- Platelet count <50,000/μL (50 x 109/L) with bleeding or before a non-neurologic invasive procedure or minor surgery.
- Platelet count <100,000/μL (100 x 109/L) in a sick premature infant or before a neurologic invasive procedure or surgery, cardiovascular surgery, or other major surgery;
- Qualitative platelet defect with bleeding, prior to an invasive procedure or surgery.
- Platelet count 80,000-100,000/μL (80-100 x 109/L) before or during an ECMO procedure, or with unexplained severe bleeding.

Notably, there is no obvious link between the seriousness of thrombocytopenia and significant bleeding incidents such intracranial hemorrhage (ICH) (37).

Patients > 4 month of age

- Patients with hypo proliferative thrombocytopenia should get prophylaxis if platelate count is <10,000μL ($10x10^9$/L).
- If an invasive surgery cannot be delayed, patients with a platelet count of at least 50,000/μL (50 x 109/L) should receive prophylaxis.
- Prior to some ophthalmologic and neurosurgical procedures, a platelet count of 100,000/μL (100 x 109/L) is advised.
- For ECMO procedures, or in cases of unexplained severe bleeding during the surgery, a platelet count of 80,000/μL (80–100 x 109/L) is advised.

By getting a platelet count 10–60 minutes after each transfusion, the response to platelet transfusions should be kept in track. Platelet refractoriness is shown by low post-transfusion platelet count increments (CCI 7.5 x 109/L) after two or more consecutive transfusions of ABO-compatible platelets (35).

Patients with genetic or acquired platelet function problems may benefit from pharmacological treatment with an anti-fibrinolytic, desmopressin acetate, or rFVIIa.

Table 5. Summary for suggested transfusion thresholds for platelet transfusion

Platelet <20 -30 x 10^9 /L	In the absence of bleeding
Platelet <50 x 10^9 /L	Bleeding, current coagulopathy, planed surgery or exchange transfusion
Platelet <100 x 10^9 /L	Major bleeding, major surgery

Indication for transfusion of FFP

- For exchange transfusion for reconstitution of RBCs.
- Multiple or singular coagulation factor deficiencies.
- Support in disseminated intravascular coagulation (DIC) treatment.
- Vitamin K deficiency or liver disease.
- While awaiting plasma exchange in thrombotic thrombocytopenic purpura (TTP).
- Clinical evidence of coagulopaty in bleeding patients.

- Replacement therapy when a specific factor concentrate is not available for congenital antithrombin deficiency, protein C deficiency, or protein S deficiency.
- To replace clotting factors as part of a massive transfusion protocol (for instance, in cases of severe trauma, surgical bleeding, fetomaternal hemorrhage, or ECMO).
- Reversal of warfarin in patients with ongoing bleeding or those who urgently require an invasive treatment, albeit safety and effectiveness in pediatric patients have not been shown.

As tolerated, a plasma dosage of 10-15 mL/kg is usually given. Any component or pool's total administration time cannot go beyond 4 hours. In the absence of consumption (DIC), a plasma dosage of 10-15 mL/kg is anticipated to result in a 15-20% increase in clotting factors (38).

Indications for transfusion of cryoprecipitate

- Dysfibrinogenemia or hypofibrinogenemia (fibrinogen 100–150 mg/dL) brought on by a lack of synthesis (liver illness), consumption (DIC), dilution (large transfusion) or dilution with bleeding, or occurring prior to surgery when fibrinogen concentrate is unavailable or not required.
- Von Willebrand disease with bleeding, before an invasive procedure or preoperatively, when factor concentrate containing von Willebrand factor is not available and dezmopressin is ineffective or contraindicated (a fibrinogen concentrate is approved in the US for treatment of congenital fibrinogen deficiency).
  Note: desmopressin is contraindicated for children < 2 years of age.
- If a specific clotting factor concentrate is not immediately accessible and desmopressin is ineffective or contraindicated, hemophilia A with bleeding or before an invasive surgery.
- When an FDA-approved Factor Xlll concentrate is not immediately available, replacement therapy is used for the following situations:factor XIII deficiency with bleeding.
- Making fibrin sealant (if pathogen-inactivated fibrin sealant is not readily available).

In the absence of consumption, the recommended dosage of cryoprecipitate is 1-2 units/10 kg, which is predicted to increase fibrinogen by 60-100 mg/dL (38).

Conclusion

It is evident from a review of these papers that there is no solid agreement on the precise indications for transfusion of pediatric patients. To treat perioperative bleeding in pediatric patients, institutional protocols based on recommendations must be devised while taking into account the local resources available. It is necessary to check the patient's valemic condition and replace blood in a target-oriented manner. Massive bleeding requires consideration of the danger of coagulopathy and prompt achievement of hemostasis. The care of critically ill children requires fluid resuscitation. Fluid administration that is appropriate and timely is essential for the best results and recommendations are shifting to a more evidence-based individualized approach

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