

**New York State Council on  
Human Blood and Transfusion Services**

***GUIDELINES FOR TRANSFUSION  
OF PEDIATRIC PATIENTS***

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**2016**

**New York State Council on Human Blood and Transfusion Services  
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Empire State Plaza - P.O. Box 509  
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# Guidelines for Transfusion of Pediatric Patients

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# NEW YORK STATE COUNCIL ON HUMAN BLOOD AND TRANSFUSION SERVICES

## GUIDELINES FOR TRANSFUSION OF PEDIATRIC PATIENTS

### INTRODUCTION

This document combines the Council's existing "Guidelines for Transfusion Therapy of Infants from Birth to Four Months of Age," 3<sup>rd</sup> edition, 2012, with additional guidance pertaining to older pediatric patients. Throughout the document, sections that apply only to infants < 4 months of age are marked. Several pediatric transfusion guidance documents were reviewed, as well as subspecialty articles in the field. A comparison of these publications makes it clear that a firm consensus is lacking regarding definitive indications for transfusion of pediatric patients.

Informed consent for transfusion is necessary and must be documented. This should be separate from documentation of consent for any other treatment. See the Council's "Recommendations for Consent for Transfusion," 2<sup>nd</sup> edition, 2008. New York State has neither a standard form for documenting consent nor a requirement for the frequency. Specifications for informed consent are the purview of each transfusion facility. However, it is recommended that documentation be placed in the patient's chart, signed by the authorized provider ordering the transfusion, attesting that the indications, risks (including possible fatal adverse effects), benefits, estimated number of, and alternatives to, transfusion have been explained to a patient's parent(s) or authorized surrogate. Documentation of the indications should include pertinent patient signs and symptoms, as well as laboratory testing results. The parent's or surrogate's consent or refusal should be acknowledged and documented in the chart, consistent with the policies of the transfusion facility. If transfusion is refused, subsequent actions taken should be consistent with the urgency of the need for transfusion, the facility's policies, New York State regulations applicable to the patient's age, and other circumstances pertaining to the particular patient.

Transfusion therapy must be individualized, based on each child's clinical status. These guidelines set forth acceptable clinical circumstances under which transfusion may be given, but are not intended to be absolute indications for transfusion. Special clinical circumstances not covered by the guidelines may make transfusion therapy appropriate, and treatments included in these guidelines may not necessarily be clinically beneficial for a given patient.

### I. PRETRANSFUSION TESTING AND COMPATIBILITY CONSIDERATIONS

#### A. Patients < 4 Months of Age

1. An initial pretransfusion specimen from the infant must be tested for ABO group (forward grouping only) and Rh type (cord blood or heelstick specimen).
2. An initial antibody screen must be done using a sample from either the infant or the mother. If no unexpected antibodies are detected initially, the red blood cell (RBC) unit should be ABO compatible with the infant and mother and either Rh negative or of the same Rh group as the infant:
  - a. repeat ABO/Rh grouping is not required;

- b. repeat antibody screening is not required; and
- c. compatibility testing is not required.

*Note: Before transfusing non-group O RBCs to an infant, it is necessary to test the infant's serum for passively acquired anti-A and anti-B antibodies. If (maternal) IgG anti-A or anti-B antibodies are detected, ABO-compatible RBCs should be transfused until antibody is no longer demonstrable in the infant's serum; it is not necessary to perform compatibility tests on these units. If the infant is discharged and readmitted, then repeat ABO/Rh and antibody screen are required.*

3. Compatibility testing is required only under the following conditions (the mother's serum may be used):
  - the infant has an unexplained positive direct antiglobulin test result (e.g., not due to Rh immune globulin); or
  - an unexpected antibody is detected in the infant's or mother's serum or, alternatively, antigen-negative blood may be used without compatibility testing.

## **B. Patients $\geq$ 4 Months of Age**

1. An initial pretransfusion specimen from the patient must be tested for ABO/Rh and screened for unexpected antibodies. If no unexpected antibodies are detected, an immediate spin crossmatch or computer crossmatch (if the blood group has been verified by a repeat sample or from prior history) may be performed with an ABO- and Rh-compatible RBC unit.
2. Compatibility testing, including indirect antiglobulin phase, and selection of antigen-negative RBCs (if applicable), are necessary under the following conditions:
  - an unexpected antibody is detected in the patient's serum;
  - the patient has a positive direct antiglobulin test result; or
  - the patient has a history of an antibody, not detectable currently.

## **II. RED BLOOD CELLS (RBCs)**

### **A. Simple Transfusion**

There is no single hemoglobin (Hb) trigger that indicates a need for RBC transfusion. Clinical evaluation is paramount. The major indication for RBCs is a need to increase red blood cell mass and improve oxygen delivery in patients with anemia and to replace blood volume in intravascular volume depletion from acute blood loss or systemic disease. A rarer indication is to suppress endogenous hemoglobin and red blood cell production in selected patients with thalassemia or sickle cell disease (SCD). Table 1 (page 19) and Table 2 (page 20) present some guidelines for transfusion of pediatric patients. The differences in patient size and blood volume, along with differences in acceptable levels of anemia in response to stress contribute to the distinction between adult and pediatric transfusions. In older children, the indications for transfusion may be similar to those for adults, but one should take into account the difference in blood

volume, the ability to tolerate blood loss, and the normal hemoglobin of the age group in question. RBCs are indicated in the management of acute hemolytic anemia, and/or bone marrow failure in the presence of cardiac or respiratory dysfunction. RBCs are not indicated to manage nutritional anemia or when normal cardiac and respiratory functions are maintained.

See Table 1: Guidelines for Transfusion of RBCs in Patients < 4 Months of Age (page 19)

See Table 2: Guidelines for Transfusion of RBCs in Patients ≥ 4 Months of Age (page 20)

A randomized controlled trial in stable critically ill children found that a restrictive Hb trigger (7.0 g/dL) was as safe and effective as a liberal Hb trigger (9.5 g/dL). (See Lacroix *et al.*) This has not been extrapolated to unstable patients and a higher threshold has been considered for children with cardiorespiratory compromise and/or symptoms of anemia.

The usual dose of RBCs administered is 10-15 mL/kg, as tolerated. The rate of infusion depends on the type of component, the total volume to be infused, venous access, and the patient's intravascular fluid tolerance. The largest gauge needle appropriate for the patient should be used. Small volume red cell transfusions are usually infused over a 2-4 hour period. Total duration of administration for any component must be ≤ 4 hours.

Large-volume RBC transfusions should be administered using an infusion device, within a 4-hour time frame, as tolerated. If the duration of the transfusion is to exceed 4 hours, the blood component should be subdivided, and the second portion stored in the blood bank until needed.

For RBC transfusions, the expected response to a standard dose depends on the concentration of red blood cells in the component, which varies based on the anticoagulant/preservative solution used. RBCs with a hematocrit ≥ 80%, such as those in CPD or CPDA-1, would be expected to result in an increment of 3 g/dL. Those in an additive solution, with a hematocrit of approximately 60%, would be expected to result in an increment of 2 g/dL. Evidence suggests that small-volume transfusions containing additive solution are safe for use in infants and older children. The dose may need to be adjusted depending on the patient's clinical condition, the desired hemoglobin increase, and the concentration of red blood cells in the component.

*Red blood cell replacement calculation:*

*Volume required = TBV x desired Hct increase/Hct of RBC unit*

*TBV: total blood volume*

*Hct: Hematocrit*

*Example (using an additive solution component):*

For a 10 kg child:

TBV = 75 mL/kg body weight = 750 mL;

Initial Hct is 19%; Desired Hct is 25%;

$(750 \text{ mL} \times (25\% - 19\% / 60\%)) = 75 \text{ mL}$  of RBCs are needed.

*Note: Blood volume is higher in term newborns (approximately 85 mL/kg) and preterm infants (approximately 100 mL/kg) than in older children.*

## **B. Exchange Transfusion in Infants**

Severe hemolytic disease of the fetus and newborn (HDFN) or progressive hyperbilirubinemia from other causes posing a risk for kernicterus are the usual indications for exchange transfusion. In the event that exchange transfusion is necessary, the following have been recommended:

1. RBCs should be hemoglobin S negative, leukoreduced,  $\leq 7$  days old, and CMV reduced risk. Irradiation is essential if the infant has undergone intrauterine transfusion, in order to reduce the risk of transfusion-associated graft-vs-host disease (TA-GVHD). See Section VIII.C. (page 16).
2. The RBCs should be group O or ABO group-compatible with the infant and the mother, be Rh negative or Rh identical with the infant, and lack the red cell antigens to which the mother has made alloantibodies. RBCs should be crossmatch compatible with the infant's serum. If an adequate infant sample is unavailable, or in the presence of significant maternal red cell alloantibodies, it may be necessary to demonstrate crossmatch compatibility with maternal serum, or with the infant's red cell eluate, if the infant has a positive direct antiglobulin test.
3. CPD, CPDA-1 and additive solution (with supernatant removed) packed RBCs reconstituted with thawed fresh frozen plasma (FFP) have been used for exchange. The plasma should be ABO compatible with the infant. The RBCs are usually reconstituted to the desired hematocrit (generally to approximately 45%) to reduce the risk of post-exchange polycythemia and hyperviscosity. During partial exchange transfusion for polycythemia, crystalloid may be used instead of FFP.

## **C. Extracorporeal Membrane Oxygenation (ECMO)**

ECMO is a form of heart-lung bypass for treating reversible pulmonary disease or temporary cardiac dysfunction. Large-volume RBC, plasma, and platelet transfusions may be required.

Components used do not require irradiation unless the patient falls into a high risk category for TA-GVHD or the component used places the patient at higher risk for the development of TA-GVHD. See Section VIII.C. (page 16). There is one documented case of GVHD in a patient undergoing ECMO.

The recommendations in Section II.B. above regarding blood components for exchange transfusion also apply to ECMO. Also see information on page 8 regarding platelet transfusion in association with ECMO.

## **D. Intrauterine Transfusion**

Intrauterine RBC and platelet transfusions are usually considered for severe fetal anemia due to intrauterine blood loss of either a hemorrhagic or immunohematologic nature, such as severe Rh hemolytic disease or severe fetal thrombocytopenia associated with fetal/neonatal alloimmune thrombocytopenia (FNAIT). RBCs should be as fresh as possible, group O, hemoglobin S negative, crossmatch compatible with the mother's serum, and have an adjusted hematocrit (70%-80%) and RBC mass intended to achieve the desired therapeutic effect while minimizing the

volume used. In the case of FNAIT, platelets should be either crossmatch compatible or negative for the antigen to which the mother has an antibody. Additionally, intrauterine RBC and platelet transfusions should be CMV reduced risk (seronegative and/or leukoreduced) and irradiated. Any blood component transfused during the postnatal hospitalization, whether an exchange transfusion, supplemental RBC transfusion, or platelet transfusion, should also be irradiated. See Section VIII.C. (page 16).

### **III. Sickle Cell Disease (SCD) and Other Hemoglobinopathies**

#### **A. Rationale for Transfusion Therapy in SCD**

There have been several observational studies and clinical trials that have demonstrated the benefit of transfusion therapy for the prevention and management of some complications associated with SCD. This is particularly true for chronic transfusion therapy for the prevention of initial and recurrent stroke in patients at high risk. The numbers of trials for various complications are limited; therefore, recommendations for transfusion are frequently based on expert consensus (see Table 3, page 21). There are several conditions for which transfusion is not recommended; these include uncomplicated painful crisis, asymptomatic anemia, acute renal failure, and priapism, unless associated with surgery.

The primary goals of transfusion therapy are to:

- Improve symptomatic anemia and oxygen carrying capacity;
- Reduce the percentage of circulating red blood cells with high concentrations of HbS; and
- Reduce and prevent acute complications.

#### **B. Types of Transfusion in SCD**

##### **1. Episodic/acute transfusion**

- a. Episodic/acute transfusion of one or more RBC units over a short period of time to manage or interrupt some acute complications of SCD.

##### **2. Chronic transfusion**

- a. Chronic transfusion is utilized when there is ongoing risk of morbidity from a complication of SCD that outweighs the risk of the complications of prophylactic long-term transfusion. In chronically transfused patients with SCD, especially those with SCA, transfusions are performed every 3-6 weeks, with a primary goal of maintaining HbS < 30% until the next transfusion. The transfusion goal for prevention of recurrent stroke may be relaxed to < 50% HbS after a few years free of neurologic sequelae; however, transfusions cannot be safely discontinued.
- b. Patients should be monitored appropriately if a chronic transfusion protocol is used.

#### **C. Methods of Transfusion in SCD**

##### **1. Simple transfusion**

- a. The patient receives  $\geq$  RBC units without removal of any patient blood.

- b. This method will increase Hb\Hct and decrease HbS % in a heterocellular fashion, but not to the extent as exchange transfusion.

It is important to limit hemoglobin concentration to  $\leq 10$  g/dL in patients with SCA who are not chronically transfused, because patients may be at risk for hyperviscosity as a result of a high percentage of circulating HbS-containing red blood cells.

## 2. Exchange transfusion

- a. Life-threatening complications, such as an acute neurological event or severe acute chest syndrome, may require emergent intervention to rapidly reduce the HbS concentration. This is most effectively achieved by RBC exchange transfusion.
- b. The goals of exchange transfusion include:
  - rapidly reducing HbS cells to  $< 30\%$ ;
  - eliminating the risk of increased viscosity; and
  - reducing the risk of iron accumulation.
- c. Exchange transfusion may be performed manually, whereby whole blood is removed and replaced with donor RBCs with or without saline.
- d. Automated erythrocytapheresis, usually performed by centrifugation, separates out the patient's red blood cells and returns the patient's remaining components along with donor HbA RBCs.

Automated techniques require knowing the patient's height, weight, desired amount of HbS cells remaining (usually  $< 30\%$ ) and desired final Hct (usually 28-30%). A larger number of RBC units are usually required for this process.

## D. Alloimmunization in SCD

A major complication of chronic transfusion therapy in SCD and other hemoglobinopathies is alloimmunization to red cell antigens. The most common clinically significant antibodies encountered are to Rh (E, C) and Kell antigens. Manifestations of delayed hemolytic transfusion reactions can sometimes mimic features of a painful crisis in SCD. It is important to obtain a red cell antibody history carefully, because many antibodies may be transient and not detectable at all times. If red cell antibodies have developed, the patient's physician should be informed, including which antibodies have been made. It is recommended that the patient's parent(s) also be informed.

Prior to initiation of transfusion therapy, it is important to perform extended antigen phenotyping to facilitate identification of antibodies that may develop in the future. If the patient has been transfused within the last 3 months, genotyping may be performed or a hypotonic wash may be utilized for the antigen typing. Red blood cells from sickle cell patients are resistant to hypotonic washing, whereas RBCs from normal persons (e.g. donors) will lyse when subjected to hypotonic conditions (see Brown). This allows separation of autogeneic red blood cells from donor RBCs for the purposes of phenotyping. Prospective limited matching for C, E, and Kell antigens has been shown to reduce the incidence of alloimmunization. However, currently there is no well documented evidence to support the routine use of extended phenotype-matched RBCs (i.e. matching other antigens, in addition to C, E, and Kell) for clinical benefit in all patients with SCD. Because of limited supply, extended phenotype-matched RBCs

should be reserved first for those patients who have made alloantibodies.

### **E. Hyperhemolytic Syndrome**

Hyperhemolytic syndrome is a sudden or acute drop of hemoglobin below the pre-transfusion value following a transfusion. There is accelerated destruction of both autogeneic and donor red blood cells. Alloantibodies with or without autoantibodies to red cell antigens are often seen, but the absence of new alloantibodies does not rule out hyperhemolysis. The syndrome has occurred even after the transfusion of phenotypically-matched RBCs and is often associated with reticulocytopenia.

If hyperhemolysis is suspected, there should be consideration of discontinuing transfusion and administering intravenous gamma globulin (IVIG) with steroids.

### **F. Recommended RBC Component Attributes in SCD**

- HbS-negative;
- Leukoreduced to prevent HLA sensitization and to reduce the risk of FNHTR;
- Limited phenotype matching for all patients: C, E, and Kell antigens, as applicable, to reduce alloimmunization to red cell antigens; and
- Extended phenotype matching for patients with red cell alloantibodies.

### **G. $\beta$ -Thalassemia (Major and Intermedia)**

Homozygous  $\beta$ -thalassemia is marked by profound anemia (Hb of 3-4 g/dL). Cardiovascular compromise ensues and excessive marrow expansion impairs linear growth of bones, leading to reliance on RBC transfusions. Thalassemia intermedia has a more variable hematologic picture. The anemia can be moderate to severe, with Hb concentrations ranging from 6-9 g/dL, prompting variable transfusion needs.

The primary goal of transfusion therapy in patients with  $\beta$  thalassemia is suppression of the erythropoietic drive, to ensure that growth and development are adequate throughout childhood. Transfusions are typically needed every 3-4 weeks in patients with thalassemia major, but can be intermittent or as infrequent as every 6-8 weeks in thalassemia intermedia. Pre-transfusion hemoglobin concentrations are usually maintained at 9-10 g/dL. As in SCD, extended antigen typing should be performed prior to initiation of transfusion therapy and leukoreduced RBCs should be utilized.

## **IV. PLATELETS**

Platelets for transfusion are available in two forms: pools of whole blood-derived platelet concentrates and platelets collected via apheresis. Platelet concentrates are prepared from donated whole blood, are separated within 8 hours of collection, and generally contain a minimum of  $5.5 \times 10^{10}$  platelets. These are usually pooled prior to issuance. In New York, apheresis platelets are collected from a single donor who has not taken aspirin in the previous 3 days; such components contain a minimum of  $3 \times 10^{11}$  platelets suspended in 200-300 mL of plasma. Platelets with additive solution (PAS) and pathogen-inactivated platelets are now available, and may offer advantages for some pediatric patients.

## A. Patients < 4 Months of Age

### 1. Indications for platelet transfusion:

- Platelet count < 20-30,000/ $\mu\text{L}$  ( $20-30 \times 10^9/\text{L}$ ) in infants lacking platelet production;
- Platelet count < 50,000/ $\mu\text{L}$  ( $50 \times 10^9/\text{L}$ ) with bleeding, or prior to a non-neurologic invasive procedure or minor surgery;
- Platelet count < 100,000/ $\mu\text{L}$  ( $100 \times 10^9/\text{L}$ ) in a sick premature infant or prior to a neurologic invasive procedure or surgery, cardiovascular surgery, or other major surgery;
- Qualitative platelet defect with bleeding, prior to an invasive procedure or surgery, or with unexplained excessive bleeding during cardiopulmonary bypass; and
- Platelet count < 80,000-100,000/ $\mu\text{L}$  ( $80-100 \times 10^9/\text{L}$ ) prior to or during an ECMO procedure, or with unexplained excessive bleeding during the procedure.

*Note: There is no clear correlation between the severity of thrombocytopenia and major bleeding events, such as intracranial hemorrhage (ICH).*

### 2. Immune thrombocytopenias during the neonatal period

#### a. Fetal and neonatal alloimmune thrombocytopenia (FNAIT)

- 1) FNAIT is caused by maternal anti-platelet antibodies that cross the placenta and interact with fetal platelets. The vast majority of cases are due to antibodies to HPA-1a (80-90% of cases), HPA-5b, or HPA-3a.
- 2) Platelet transfusion is the treatment of choice for infants born with severe thrombocytopenia - < 30,000/ $\mu\text{L}$  ( $30 \times 10^9/\text{L}$ ), particularly those with clinical evidence of bleeding.
- 3) Platelet components should be CMV reduced risk, irradiated, and either negative for the platelet antigen to which the mother has antibodies or crossmatch compatible.
- 4) If antigen-negative or compatible platelets are not immediately available, a trial of random donor platelets should be given to infants. IVIG can also be administered in order to potentially prolong incompatible platelet survival and shorten the period of thrombocytopenia (spontaneous recovery occurs in 1-6 weeks).
- 5) If there is a poor response to random donor platelets and compatible platelets are not available, it may be necessary to collect platelets from the mother. Such platelets should be irradiated and the plasma reduced to prevent passive transfer of maternal antibodies. Infectious disease testing may be waived with the written authorization of the medical director of the transfusion service, per 10 NYCRR, Section 58-2.3(d).
- 6) Moderate thrombocytopenia -  $\geq 30,000/\mu\text{L}$ -50,000/ $\mu\text{L}$  ( $30- 50 \times 10^9/\text{L}$ ), without any obvious evidence of hemorrhage may be managed with IVIG treatment.

## 7) Management of subsequent pregnancies

- a) The management of subsequent “at-risk” pregnancies is influenced by the history of previous fetal/infant morbidity and/or mortality (a full discussion is beyond the scope of this guideline; refer to Pacheco *et al*, Peterson *et al*, Delbos *et al*). There is an increased trend toward a non-invasive approach to management, rather than obtaining a fetal platelet count, with various algorithms based on the previous history. Prenatal management has utilized administration of IVIG and steroids to the mother, at different doses and schedules, depending on the history. There is recent evidence that the number of gestations is predictive of ICH in anti-HPA-1a- alloimmunized mothers. It was suggested that other immunologic factors may influence the risk of ICH and possible response to therapy, which may require further investigation. (See Delbos *et al*.)
- b) If cordocentesis is necessary to obtain a fetal sample for a platelet count, a compatible platelet component should be available. Such a component would need to be CMV reduced risk and irradiated.
- c) In the case of antepartum maternal donation of platelets, all routine tests appropriate for neonatal transfusions should be performed, and the unit may be transfused, provided it meets the other criteria for allogeneic donation. Platelets should be irradiated and plasma reduced to prevent passive transfer of maternal antibodies.

### b. Thrombocytopenia due to maternal autoantibodies (maternal ITP)

- 1) IVIG, with or without steroids, is generally useful to increase the platelet count and prolong platelet survival in this self-limiting disorder.
- 2) Platelet transfusion is not indicated in the absence of life-threatening bleeding.

## B. Patients $\geq$ 4 Months of Age

### 1. Indications for platelet transfusion:

- Prophylaxis in a patient with a platelet count  $< 10,000/\mu\text{L}$  ( $10 \times 10^9/\text{L}$ ) due to hypoproliferative thrombocytopenia;
- Prophylaxis in a patient with a platelet count  $< 50,000/\mu\text{L}$  ( $50 \times 10^9/\text{L}$ ) prior to an invasive procedure if that procedure cannot be postponed. A platelet count  $\geq 100,000/\mu\text{L}$  ( $100 \times 10^9/\text{L}$ ) is recommended prior to neurosurgical and some ophthalmologic procedures; and
- Platelet count  $< 80,000\text{-}100,000/\mu\text{L}$  ( $80\text{-}100 \times 10^9/\text{L}$ ) prior to or during an ECMO procedure, or with unexplained excessive bleeding during the procedure.

### 2. Administration of platelets at a predetermined ratio in massive transfusion

In order to overcome the depletion of coagulation factors associated with massive transfusion, many institutions have developed a massive transfusion protocol for specific groups of patients with trauma. These protocols specify the administration of blood components in a predetermined ratio that approximates the composition of

whole blood. The optimal ratio at which components should be administered to pediatric patients has not been determined and the efficacy in pediatric trauma has not been fully evaluated.

3. Intrinsic or acquired platelet dysfunction with bleeding or prior to an invasive procedure

Patients with congenital platelet dysfunction, such as Glanzmann's thrombasthenia, Bernard-Soulier syndrome, or storage pool disease, often have bleeding beginning at an early age and usually require platelet transfusion to treat severe bleeding.

In platelet-type von Willebrand disease (vWD), platelet transfusion is the treatment of choice. However, platelet transfusion is not indicated as a treatment for other forms of vWD, although desmopressin acetate (DDAVP) may be of use (see the Council's "Guidelines for the Administration of Cryoprecipitate," 4<sup>th</sup> edition, 2012). In severe disease, a concentrate containing von Willebrand factor, such as Antihemophilic Factor/von Willebrand Factor Complex (Humate P), may be indicated.

Patients with platelet function disorders, whether hereditary or acquired, may respond to pharmacologic intervention with an anti-fibrinolytic, DDAVP, or rFVIIa.

4. Active microvascular bleeding attributed to platelet dysfunction

This group includes thrombocytopenic cardiac surgery patients with ongoing abnormal microvascular bleeding in whom no surgical cause can be identified. Such patients usually have a qualitative platelet abnormality believed to contribute to a bleeding tendency, even if the platelet count is normal.

In patients with acquired reversible platelet dysfunction in the setting of renal insufficiency, treatment with dialysis, DDAVP, erythropoietin, or transfusion of RBCs (to reach a hematocrit of 30%) may be employed as a therapeutic strategy for bleeding. Cryoprecipitate may be effective in some patients if DDAVP is unavailable, ineffective, or contraindicated. Platelet transfusion is not considered useful because transfused platelets are also affected by the uremia and thus will become dysfunctional.

In the case of drug-induced platelet dysfunction associated with bleeding, the responsible drug should be discontinued prior to elective surgery. Platelet function usually returns to normal within 1 week after the responsible agent has been withdrawn. Platelet transfusion for urgent reversal may be indicated, based on the reversibility and half-life of the anti-platelet agent and type of surgical procedure.

5. In the absence of life-threatening bleeding, platelet transfusion **is not indicated** in cases of immune thrombocytopenia purpura (ITP), post-transfusion purpura (PTP), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or heparin-induced thrombocytopenia (HIT).

### C. Platelet Dosing and Administration

The usual dose of platelets is 5-10 mL/kg (the same dose for pooled platelet concentrates and apheresis platelets), as tolerated. The rate of infusion depends on the type of component, the total volume to be infused, venous access, and the patient's intravascular fluid tolerance. Platelet transfusions may be transfused more rapidly if the patient's cardiovascular status is stable. Total duration of administration for any component or pool must not exceed 4 hours.

The plasma of the component should be ABO and Rh compatible with the recipient's red blood cells, except in emergent situations.

*Note: Development of a positive direct antiglobulin test and/or hemolysis has been reported in cases in which group O platelets with high-titer IgG ABO antibodies (usually anti-A or anti-A,B) have been transfused to a patient who is not group O (usually group A). For infants and children, the plasma of platelet components should be ABO compatible with the recipient's red cells. If it is necessary to transfuse platelets whose plasma is ABO incompatible with the recipient's red cells, particularly group O platelets to a group A patient, it is recommended that the anti-A or anti-B antibodies present in the plasma of platelet components be titrated and low-titer components be used. Alternatively, the amount of incompatible antibody can be reduced by washing or centrifugation to reduce the volume of supernatant plasma present.*

An unpooled unit of whole blood (WB)-derived platelets contains, on average, 0.036 mL of RBCs. Although the risk of alloimmunization is low (< 4% of patients), Rh-negative patients who receive Rh-positive WB-derived platelets should be considered candidates for Rh immune globulin (RhIG), especially if the recipient is female, to prevent sensitization to the D antigen. A 300 µg dose of RhIG, with a half-life of 21 days, offers protection for 15 mL of Rh-positive RBCs.

The RBC contamination in apheresis platelets is very low (< 0.01 mL/unit). Many physicians do not administer RhIG for apheresis platelets.

### D. Assessment of Response to Platelet Transfusion

Transfusion of usual dose is expected to increase the platelet count by 50,000-100,000/µL (50-100 x 10<sup>9</sup>) in a non-refractory patient, depending on the actual number of platelets present, which is variable based on the preparation method.

In order to assess the patient's response to the transfusion, a post-transfusion platelet count should be performed within 60 minutes after completion of the transfusion. A corrected count increment (CCI) can be calculated based on the patient's post transfusion platelet count 10-60 minutes after transfusion, the patient's body surface area and the number of platelets administered (see below) to determine whether the patient's response was the expected increment, a suboptimal increment, or may suggest a refractory state.

*Corrected count increment:*

$$CCI = \frac{(\text{posttransfusion count} - \text{pretransfusion count}) \times \text{body surface area (M}^2\text{)}}{\text{\# of platelets transfused}}$$

*Example of calculation of # of platelets transfused (using minimum platelet content/unit and hypothetical unit volume) to a 2 kg infant receiving 10 mL/kg (20 mL)*

Apheresis platelet unit =  $3 \times 10^{11}/300 \text{ mL} \times 20 \text{ mL} = 2.0 \times 10^{10}$  platelets transfused

WB-derived platelet unit =  $5.5 \times 10^{10}/50 \text{ mL} \times 20 \text{ mL} = 2.2 \times 10^{10}$  platelets transfused

## **E. Refractoriness to Platelet Transfusion**

Development of platelet refractoriness due to alloimmunization to HLA or platelet-specific antigens is an inherent risk for patients on chronic platelet transfusion therapy. Leukoreduced cellular blood components reduce the risk of HLA alloimmunization. Apheresis platelets and leukoreduced pooled whole blood-derived platelet concentrates are considered equivalent in the prevention of HLA alloimmunization. The response to platelet transfusions should be monitored by obtaining a platelet count 10-60 minutes after each transfusion. Poor post-transfusion platelet count increments ( $\text{CCI} < 7.5 \times 10^9/\mu\text{L}$ ) following 2 or more consecutive transfusions of ABO-compatible platelets indicate platelet refractoriness. Patients who are refractory to platelet transfusions because of alloimmunization may benefit from HLA-matched, selected mismatched based on the patient's HLA antibodies, or crossmatch-compatible platelets. Platelets carry ABO antigens on their surface, and ABO-matched platelets have been found to survive better than those that are ABO incompatible with the recipient's plasma.

Platelet refractoriness may also be due to non-immune causes, such as massive bleeding, fever, sepsis, splenomegaly with splenic sequestration, disseminated intravascular coagulation (DIC), platelets damaged by poor storage, effects of drugs, thrombotic thrombocytopenic purpura, immunosuppressive treatment, and liver dysfunction.

## **V. PLASMA (FRESH FROZEN PLASMA [FFP] and PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY [PF24])**

### **A. Indications**

1. Reconstitution of RBCs for exchange transfusion;
2. Isolated or multiple coagulation factor deficiency, with bleeding or prior to an invasive procedure or surgery, if specific factor replacement is not possible (e.g. congenital deficiency of Factor V, II, X, or XI);

*Note: In neonates, specific guidelines and literature for PT/aPTT criteria are not well defined. The pro- and anti-coagulant factors in neonates are typically lower in activity than in adults, but they are usually balanced. For older children, guidelines for adults may be applied. In the presence of bleeding, laboratory testing may indicate a significant hemostatic defect requiring correction.*

3. Support during treatment of disseminated intravascular coagulation (DIC);
4. Liver disease or vitamin K deficiency (due to drugs, liver disease or nutrition) resulting in a coagulopathy, with bleeding, or prior to an urgent invasive procedure or surgery. Vitamin K deficiency should be reversed with oral or IV vitamin K replacement if time permits;
5. Thrombotic thrombocytopenic purpura (TTP), while awaiting plasma exchange;

6. Replacement fluid during therapeutic plasma exchange in selected conditions, such as TTP and hemolytic uremic syndrome (HUS), or if there is a need to replace clotting factors in a bleeding or preoperative patient undergoing therapeutic plasmapheresis;

*Note: Plasma should not be used routinely as a replacement fluid in therapeutic plasma exchange unless indicated, such as in TTP or HUS.*

7. Replacement therapy in congenital antithrombin deficiency, protein C deficiency or protein S deficiency, when specific factor concentrate is not available;
8. Clinical evidence of coagulopathy in a bleeding patient when laboratory results are pending;
9. As part of a massive transfusion protocol to replace clotting factors (e.g. major trauma, surgical bleed, fetomaternal hemorrhage, ECMO); and
10. Reversal of warfarin in patients with active bleeding or those with an urgent need for an invasive procedure, although safety and efficacy have not been established in pediatric patients. A 4-factor prothrombin concentrate complex has been approved by the FDA for reversal of warfarin in a bleeding adult patient. However, safety and efficacy have not been studied in pediatric patients.

The indications for PF24 are the same as for FFP, except for reconstitution of RBCs for exchange transfusion and in Factor V deficiency.

## **B. Plasma Dosing, Administration, and Expected Response**

The plasma dose typically administered is 10-15 mL/kg, as tolerated. The rate of infusion depends on the type of component, the total volume to be infused, venous access, and the patient's intravascular fluid tolerance. Plasma may be transfused more rapidly if the patient's cardiovascular status is stable. The total duration of administration for any component or pool must not exceed 4 hours.

A 10-15 mL/kg dose of plasma is likely to increase clotting factors by 15-20% in the absence of consumption (DIC). Plasma should be ABO identical to the patient's type or compatible with the recipient's red blood cells.

## **VI. CRYOPRECIPITATE**

### **A. Indications:**

1. Dysfibrinogenemia or hypofibrinogenemia (fibrinogen < 100-150 mg/dL) due to lack of synthesis (liver disease), consumption (DIC), or dilution (massive transfusion) with bleeding, or preoperatively when fibrinogen concentrate is not available or is not indicated. (A fibrinogen concentrate is approved in the US for treatment of congenital fibrinogen deficiency.);
2. von Willebrand disease, with bleeding, prior to an invasive procedure or preoperatively, when factor concentrate containing von Willebrand factor is not available and DDAVP is ineffective or contraindicated.;

*Note: DDAVP is contraindicated for children < 2 years of age.*

3. Hemophilia A, with bleeding or prior to an invasive procedure, if specific clotting factor concentrate is not immediately available and DDAVP is ineffective or contraindicated;
4. Replacement therapy in Factor XIII deficiency with bleeding or when undergoing an invasive procedure, when FDA-approved Factor XIII concentrate is not immediately available; and
5. In the preparation of fibrin sealant (if pathogen-inactivated fibrin sealant is not available).

## **B. Cryoprecipitate Dosing, Administration, and Expected Response**

Cryoprecipitate dosage is 1-2 units/10 kg, which is expected to raise the fibrinogen by 60-100 mg/dL in the absence of ongoing consumption. Pre- and post-transfusion fibrinogen can be obtained to assess adequacy of treatment. Frequency of transfusion will depend on both the degree of fibrinogen recovery and the rate of consumption. Because of their small blood volume, neonates and small infants should receive only ABO-compatible cryoprecipitate.

## **VII. GRANULOCYTES**

### **A. Preparation**

The shelf life of granulocytes collected either by apheresis or from buffy coat is 24 hours at room temperature. The component must be ABO compatible with the recipient and a crossmatch is required. The component should be stored at room temperature without agitation and, ideally, be transfused as soon as possible after collection. Because of their short shelf life, these components may need to be released for transfusion prior to completion of testing for all infectious markers. New York State regulations, at 10 NYCRR, Section 58-2.3(e), permit use of a specimen collected prior to the donation, as permitted by the FDA. Or, alternatively, the director of the transfusion service may authorize an exception to customary testing requirements for a component uniquely suited to the patient's needs, with informed consent of the patient's parent(s) or other authorized party. Requirements pertaining to emergency release may apply. The component should be irradiated and, if indicated, CMV seronegative. Patients should be screened for HLA alloantibodies because alloimmunization can lead to a poor increment or a reaction. A patient may require HLA-matched components, if alloimmunized to HLA antigens.

The component should not be transfused within 4-6 hours of administration of the anti-fungal agent amphotericin B, in order to minimize the potential for adverse pulmonary reactions. A leukoreduction or microaggregate filter should not be used to collect or transfuse granulocytes.

### **B. Indications, Patients < 4 Months of Age**

Currently, there is no clear evidence on the appropriate dose or clinical efficacy of granulocytes for patients < 4 months of age. However, a typical dose for infants is  $1 \times 10^{10}$  cells daily for 5 days.

At present, the relative efficacy of granulocyte transfusions compared to appropriate available antibiotic therapy is controversial. In infants, granulocytes may be considered under the following circumstances:

1. Bacterial sepsis unresponsive to antibiotics in infants < 2 weeks of age with an absolute neutrophil count (ANC, to include neutrophils plus bands) < 3,000/ $\mu$ L ( $3 \times 10^9$ /L);
2. Bacterial sepsis unresponsive to antibiotics in infants  $\geq$  2 weeks of age with an ANC < 500/ $\mu$ L ( $0.5 \times 10^9$ /L);
3. Fungal infection and ANC as specified above (B.1., B.2.), according to age; and
4. Documented infection unresponsive to antibiotics in the presence of a qualitative neutrophil defect, regardless of the ANC.

### **C. Indications, Patients $\geq$ 4 Months of Age**

The minimum granulocyte dose is  $1 \times 10^{10}$  cells daily for at least 5 consecutive days, until evidence of recovery of peripheral neutrophil counts or clinical recovery from infection. Granulocyte transfusion may be considered under the following circumstances:

1. Bacterial sepsis unresponsive to antibiotics with absolute neutrophil count (ANC, to include neutrophils plus bands) < 500/ $\mu$ L ( $0.5 \times 10^9$ /L);
2. Fungal infection and ANC < 500/ $\mu$ L ( $0.5 \times 10^9$ /L);
3. Documented infection unresponsive to antibiotics in the presence of a qualitative neutrophil defect, regardless of ANC (e.g., chronic granulomatous disease); and
4. Recipients of HPC transplant in the presence of ongoing neutropenia and infection unresponsive to antibiotics, who have a reasonable chance of sustainable bone marrow recovery.

*Note: Patients who may receive HPCs from a sibling or parent should not receive granulocytes from a related donor, in order to prevent sensitization to HLA antigens.*

## **VIII. SPECIAL CONSIDERATIONS**

### **A. RBC Age, Preservatives, Hemoglobin S Status**

During RBC storage, there is an increase in potassium leakage from within the RBCs into the supernatant. Packed RBCs of any age are acceptable for small volume transfusions (approximately 15 mL/kg), unless there is a specific concern about hyperkalemia, which is generally not a problem for transfusions  $\leq$  25 mL/kg. However, hyperkalemia may be a concern when units/components have been irradiated. See page 16. Multiple studies have shown that small-volume transfusions given over 2-3 hours cause no change in potassium concentration and several studies have shown that potassium re-equilibrates into red cells following transfusion.

RBC preservatives acceptable for small-volume transfusions include: CPD; CPDA-1; and additive solutions containing additional adenine, dextrose, and, in some cases, mannitol. The safety of additive solutions for massive or exchange transfusion has not yet been established in the US. For preterm neonates with severe renal insufficiency

requiring multiple transfusions, or for any neonate undergoing exchange transfusion, it may be desirable to remove the supernatant plasma and preservatives.

A suggestion for the use of HbS-negative RBCs in infants is based on case reports. This attribute is probably most important in exchange transfusion and other large-volume and/or rapid transfusions, as well as for transfusion of hypoxemic neonates.

## **B. Cytomegalovirus (CMV)**

Cellular blood components from CMV-seropositive donors may contain residual leukocytes that can transmit virus to seronegative patients. CMV-reduced-risk (seronegative or leukoreduced) cellular components (RBCs and platelets) should be provided to infants who weighed < 1,200 g at birth and children who are immunocompromised **AND** whose mothers are either seronegative or whose serostatus is unknown. An infant who is at risk for transfusion-transmitted CMV for any reason should receive CMV-reduced-risk cellular blood components.

If CMV seronegative, the following patients are at risk for severe morbidity and mortality for transfusion-transmitted CMV and should receive CMV-reduced risk cellular blood components:

- Patients with a congenital immune deficiency;
- Patients with AIDS;
- Patients undergoing HPC transplantation from a CMV-seronegative donor;
- Patients undergoing solid organ transplantation of lung and/or heart from a CMV-seronegative donor; and
- Female patients receiving cellular components during pregnancy.

## **C. Irradiation**

TA-GVHD has been reported in infants and other pediatric patients transfused with cellular blood components. See the Council's "Guidelines for Irradiation of Blood and Blood Components" (2012). The risk of TA-GVHD in premature infants who have received a small-volume transfusion of RBCs or platelets is unknown, although cases have been documented. Irradiation of cellular blood components with a minimum of 2,500 rads (25 Gy) is recommended in the following clinical circumstances:

- Patients with a known or suspected congenital immunodeficiency\*;
- Fetuses undergoing intrauterine transfusion, as well as all cellular components during the post-natal hospitalization;
- Patients undergoing chemotherapy, radiotherapy, or other immunosuppressive therapy;
- Patients being treated with a purine analogue drug, such as fludarabine;
- Premature infants < 1,200 g birth weight; and
- Patients undergoing allogeneic or autogeneic HPC transplantation (the HPC component itself must not be irradiated);

*Note: Treatment for a particular patient should consider the clinical condition of that patient. Post-transplant patients should continue to receive irradiated blood components until the patient's physician determines that the patient has recovered*

*immunologically and has demonstrated evidence of immune competence, by either a post-vaccination titer or an immunologic assay.*

In addition, it is recommended that the following blood components be irradiated:

- Cellular components from a blood relative\* or when the recipient and donor are members of the same genetically homogeneous group;
- HLA-matched or crossmatch-compatible platelets\*; and
- Granulocytes.

\*Required by AABB Standards

*Note: For pre-term or term infants receiving a large-volume transfusion in association with exchange transfusion or ECMO, with no risk factors as stated above, the risk of TA-GVHD and the need for irradiation must be balanced against risks due to a delay in transfusion in order to obtain an irradiated component.*

The release of potassium is increased when a component has been irradiated. If there is concern about renal insufficiency or hyperkalemia in a patient who is to receive a large-volume and/or rapid transfusion (e.g., during surgery) of RBCs that were irradiated prior to storage, measures that can be taken to minimize the potassium load include:

- using RBCs  $\leq 7$  days old;
- using washed RBCs (discard the supernatant and transfuse within 12 hours); and
- reducing the rate of infusion.

It may be advisable to avoid large-volume and rapid transfusion of stored irradiated RBCs through a central line. Insufficient published data are available on the safety of stored irradiated RBCs for either large- or small-volume transfusions, but calculations suggest that these are acceptable for small-volume transfusions (*i.e.*, those  $\leq 25$  mL/kg) infused over 2-4 hours, even on the 28-day expiration date of such a component.

#### **D. Minimizing Donor Exposures in Small Patients**

Exposure to allogeneic blood may be minimized by strictly limiting transfusion to appropriate indications, when the benefits outweigh the risks. For an infant who requires multiple small-volume transfusions, aliquots can be prepared through sterile docking of transfer bags or syringes, enabling the use of a single unit on multiple occasions.

#### **E. Blood Relatives as Donors**

Use of maternal blood for transfusion is not recommended in the absence of a specific medical indication, and blood from the father or another relative holds no advantage and may pose additional risks. Directed donation from any blood relative, including the mother, carries an added risk of immune complications, such as alloimmunization to HLA antigens and TA-GVHD. It is important that a cellular component from a blood relative, and whenever the recipient and donor are members of the same genetically homogeneous group, be irradiated to prevent TA-GVHD. See the Council's "Guidelines for Irradiation of Blood Components," 4<sup>th</sup> edition, 2012. In the scenario of a mother donating for her child, there is also the potential risk of transfusion-related acute lung injury (TRALI) due to maternal HLA and/or neutrophil antibodies directed against the child's white blood cells. Paternal blood for transfusion poses the risk of a missed

private antigen/antibody incompatibility against an RBC antigen that would not be detected in routine screening. Therefore, a full crossmatch should be performed.

**Table 1. Guidelines for Transfusion of RBCs in Patients < 4 Months of Age**

Hb < 7 g/dL with low reticulocyte count and signs of anemia\*

Acute blood loss of  $\geq$  15-20% of total blood volume

Intra-operative blood loss of  $\geq$  15% of total blood volume

Hb < 10 g/dL

- CPAP/MV with mean airway pressure < 6 cm H<sub>2</sub>O
- FIO<sub>2</sub> < 35% via oxygen hood
- On oxygen by nasal cannula
- Significant apnea or bradycardia<sup>†</sup>
- Significant tachypnea or tachycardia<sup>‡</sup>
- Low weight gain (<10 g/day over 4 days receiving  $\geq$  100 kcal/kg/day)

Hb < 12 g/dL

- CPAP/MV with mean airway pressure  $\geq$  6-8 cm H<sub>2</sub>O
- FIO<sub>2</sub> > 35% via oxygen hood

Hb < 15 g/dL with severe pulmonary or cyanotic heart disease/congestive heart failure or on ECMO

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*Abbreviations*

FIO<sub>2</sub>: fraction of inspired oxygen

TBV: total blood volume

CPAP/MV: continuous positive airway pressure/mechanical ventilation

ECMO: extracorporeal membrane oxygenation

\* Tachycardia, tachypnea, poor feeding

<sup>†</sup> > 6 episodes in 12 hours, or 2 episodes in 24 hours requiring bag and mask ventilation while on methylxanthine therapy

<sup>‡</sup> Heart rate > 180 beats/min or respiratory rate > 80 breaths/min, sustained > 24 hours

Adapted from:

Fasano R, Luban NLC. Blood component therapy. *Pediatr Clin N Am* 2008;55:421-45

Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion.

*Transfusion* 2002;42:1398.

**Table 2. Guidelines for Transfusion of RBCs in Patients  $\geq$  4 Months of Age**

Hb  $<$  7 g/dL with low reticulocyte count and signs of anemia

Acute blood loss of  $\geq$  15-20% of total blood volume

Intra-operative blood loss of  $\geq$  15% of total blood volume

Hb  $<$  8 g/dL (Hct  $<$  24%)

- in the peri-operative period, with signs and symptoms of anemia
- in congenital or acquired symptomatic anemia
- in bone marrow failure

Hb  $<$  13 g/dL with severe cardiopulmonary disease or on ECMO

Other inherited disorders of red cell production that require chronic transfusion:

- $\beta$ -Thalassemia
- Red cell aplasia (Diamond-Blackfan syndrome) unresponsive to pharmacologic therapy

Adapted from:

Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion* 2002;42:1398-1413.

**Table 3. Summary of Clinical Indications for Transfusion in SCD\***

Indication/Complication	Method of Transfusion	Recommendation Strength/Quality of Evidence <sup>‡</sup>
Infarcted stroke	Exchange or simple (acute)	Moderate/Low
Child with transcranial Doppler (TCD) > 200cm/sec	Exchange or simple (chronic)	Strong/High
Adults and children with previous clinically overt stroke	Exchange or simple (chronic)	Moderate/Low
Symptomatic acute chest syndrome (ACS) with a decrease of Hb of 1 g/dL below baseline in SCA <sup>†</sup>	Simple (Acute)	Weak/Low
Symptomatic severe ACS (defined as oxygen saturation < 90% despite supplemental oxygen)	Exchange (acute)	Strong/Low
Acute splenic sequestration plus severe anemia	Simple (acute)	Strong/Low
Hepatic sequestration plus severe anemia	Exchange or simple (acute)	Consensus/Expert panel
Intrahepatic cholestasis	Exchange or simple (acute)	Consensus/Expert panel
Multisystem organ failure (MSOF)	Exchange or simple (acute)	Consensus/Expert panel
Aplastic crisis	Simple (acute)	Consensus/Expert panel
Symptomatic anemia	Simple (acute)	Consensus/Expert panel
Prophylactic perioperative transfusion		
<ul style="list-style-type: none"> <li>Patients with SCA - transfuse to Hb of 10 g/dL prior to a surgical procedure with general anesthesia</li> </ul>	Consult SCD expert	Strong/Moderate
<ul style="list-style-type: none"> <li>Patients with HbSS, with Hb &gt;8.5 g/dL without transfusion, and receiving long term hydroxyurea therapy, who require surgery</li> </ul>	Consult SCD expert	Strong/Low
<ul style="list-style-type: none"> <li>Patients with HbSC or HbSβ+-thalassemia prior to a surgical procedure with general anesthesia</li> </ul>	Consult SCD expert	Moderate/Low

\*SCD includes genotypes HbSS, HbSβ0-thalassemia, HbSβ+-thalassemia, and HbSC.

<sup>†</sup> SCA includes genotypes HbSS and HbSβ0-thalassemia.

<sup>‡</sup> Quality of evidence based on published clinical studies (strong, moderate, low) or expert consensus

Adapted from:

Smith-Whitley K et al. *Pediatr Blood Cancer* 2012;59:358-64.

Yawn BP, et al. *JAMA* 2014;312(10):1033-48.

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