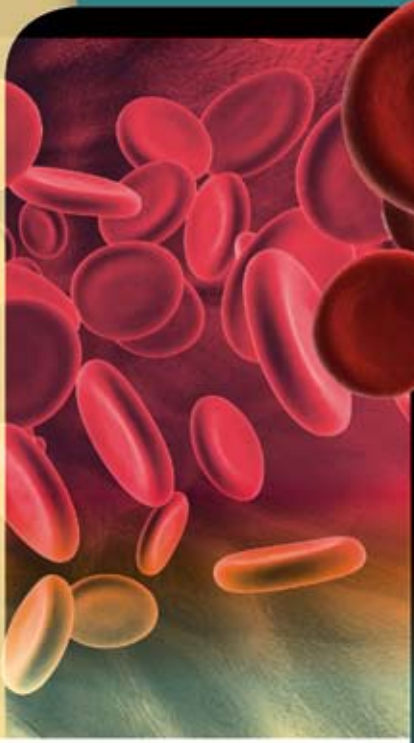
Practice Guidelines for Blood Transfusion



American Red Cross

A Compilation from Recent Peer-Reviewed Literature

Second Edition

First Edition, May 2002

Authors:
Ritchard Cable, M.D., Connecticut Region
Brian Carlson, M.D., Tennessee Valley Region
Linda Chambers, M.D., Biomedical Headquarters
Jerry Kolins, M.D., Southern California Region
Scott Murphy, M.D., Penn-Jersey Region
Lowell Tilzer, M.D., Central Plains Region
Ralph Vassallo, M.D., Penn-Jersey/NE Pennsylvania Regions
John Weiss, M.D., Badger-Hawkeye Region
Mary Ellen Wissel, M.D., Central Ohio Region

Second Edition, April 2007

Revised by:
Yvette Miller, M.D. (Chair), Arizona Region
Gary Bachowski, M.D., Ph.D., North Central Region
Richard Benjamin, M.D., Ph.D., Biomedical Headquarters
Diane K. Eklund, M.D., Northern California Region
A.J. Hibbard, M.D., Badger-Hawkeye Region
Thomas Lightfoot, M.D., New York-Penn Region
Claire Meena-Leist, M.D., Indiana-Ohio Region
NurJehan Quraishy, M.D., Western Lake Erie Region
Suneeti Sapatnekar, M.D., Ph.D., Northern Ohio Region
Jerry Squires, M.D., Ph.D., Biomedical Headquarters
Annie Strupp, M.D., Lewis and Clark Region
Ralph Vassallo, M.D., Penn-Jersey Region
John Weiss, M.D., Ph.D., Badger-Hawkeye Region

Graphic Designer: George Ramirez

Practice Guidelines for Blood Transfusion:

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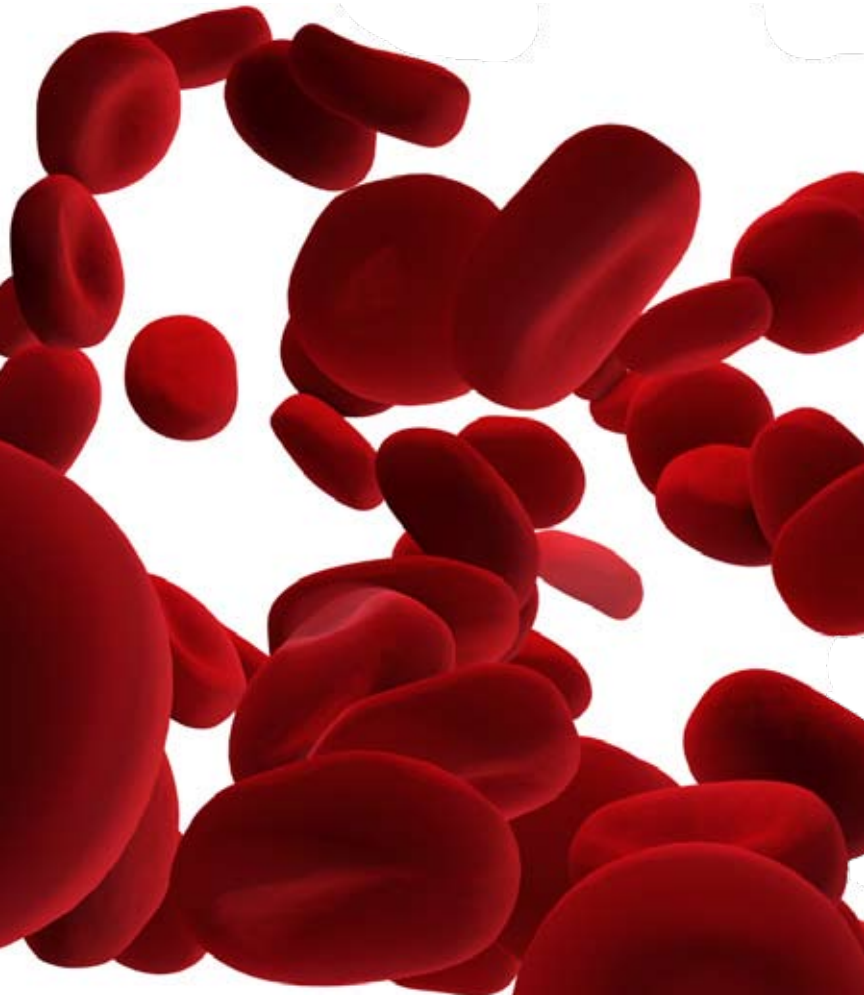
Second Edition

Users of this brochure should refer to the Circular of Information regarding the approved indications, contraindications and risks of transfusion, and for additional descriptions of blood components. Copies of the Circular of Information can be obtained from your American Red Cross region or through the AABB (internet address http://www.aabb.org). The complete text of the side effects and hazards of blood transfusion from the current Circular of Information appears in an appendix at the end of this brochure.



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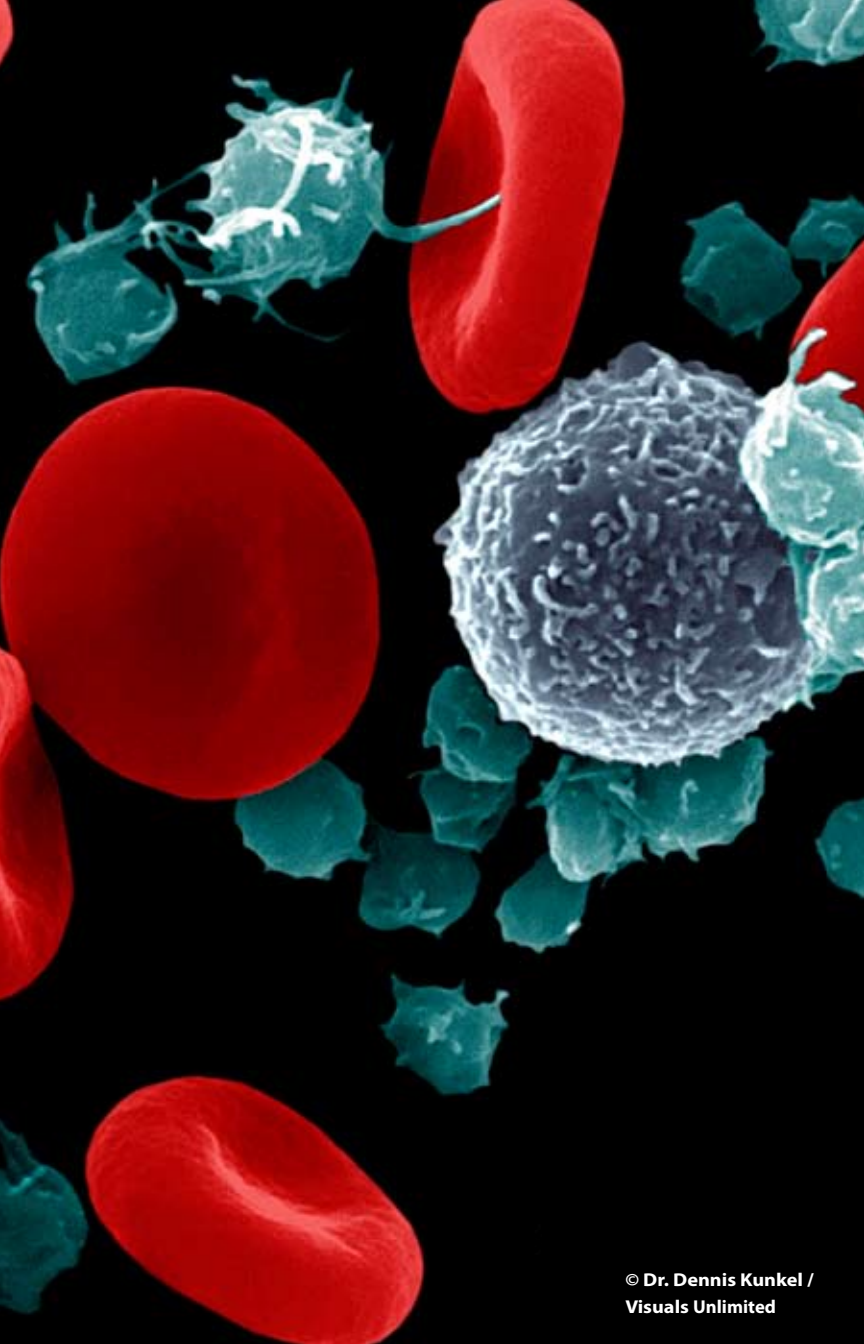
INTRODUCTION

Accrediting and regulatory agencies make specific mention of blood transfusion in a number of core functions essential to quality medical care. For example, the need for transfusion is considered one of the key parameters for determining the appropriateness of an operative procedure. An acute hemolytic transfusion reaction due to ABO incompatibility is specifically identified as a reviewable sentinel event for which a comprehensive analysis of cause, corrective action, preventive action and reporting are required. Blood transfusion is acknowledged to be a therapy that involves risks, so that the organization's performance monitoring and improvement program must address the use of blood and blood components. Furthermore, a cross functional group of medical and support staff is charged with the responsibility to take the leadership role in improving transfusion practice when indicated.

Successful performance of these functions requires that the medical staff agree to some set of practice guidelines for ordering blood transfusion. Ideally, practice guidelines would be grounded in well-designed clinical trials that clearly establish efficacy and quantify risk, in at least the most common settings in which this therapy is applied. The current literature does provide guidelines for some of the more commonly encountered clinical situations. However, variability in transfusion practice often reflects expert opinion, tradition, community practice, or personal experience.

Given the known and hypothetical risks of transfusion, as well as the cost, liability and workload involved with this therapy, there are many reasons to move the basis of transfusion practice in a particular institution away from anecdotal experience and tradition, and toward expert advice and clinical evidence. This brochure was revised in order to provide up to date blood usage guidelines from experts and expert panels, as well as the results of significant clinical transfusion trials, published in the English language in peer-reviewed journals since 2002. The authors, all of whom are physician staff for the American Red Cross, have made every attempt to fairly reproduce the advice and lessons contained in these publications. It is their hope that this brochure will be a valuable resource to hospitals who obtain blood and blood components from the American Red Cross as they develop and update their blood usage guidelines for the purpose of improving transfusion safety.



RED BLOOD CELLS | GENERAL INFORMATION

Components:

Approved name: Red Blood Cells.

Also referred to as Packed Cells, Red Cells, Packed Red Blood Cells, RBCs.

Preparation variations include Red Blood Cells (Adenine-Saline Added); Red Blood Cells Leukocytes Reduced (LR-RBC); Red Blood Cells Apheresis; Red Blood Cells Deglycerolized; Red Blood Cells Irradiated; Red Blood Cells, Low Volume; and Red Blood Cells Washed. Whole blood is rarely required and is therefore not addressed.

Description of Components:

Red Blood Cells consist of erythrocytes concentrated from whole blood donations by centrifugation or collected by apheresis method. The component is anticoagulated with citrate and may have had one or more preservative solutions added.

Depending on the preservative-anticoagulant system used, the hematocrit of Red Blood Cells ranges from about 50-65% (e.g., AS-1, AS-3, AS-5) to about 65-80% (e.g., CPDA-1, CPD, CP2D). Red Blood cells contain an average of about 50 mL of donor plasma (range 20 mL to 150 mL), in addition to the added preservative and anticoagulant solutions.

Each unit contains approximately 42.5-80 g of hemoglobin or 128-240 mL of pure red cells, depending on the hemoglobin level of the donor, the starting whole blood collection volume, and the collection methodology or further processing. When leukoreduced, RBC units must retain at least 85% of the red cells in the original component.

Each unit of Red Blood Cells contains approximately 147-278 mg of iron, most in the form of hemoglobin.

Ref. 6, 15

Selection and Preparation:

Red Blood Cells must be compatible with ABO antibodies present in the recipient serum, and crossmatched (serologic or electronic) to confirm compatibility with ABO and other antibodies prior to routine transfusion.

Extended storage preservative-anticoagulant preparations such as AS-1 and AS-3 are appropriate for nearly all patient types. Physicians concerned about preservative-anticoagulant in neonates may elect to use a different preparation (e.g., CPD or CPDA-1) or to remove preservative-anticoagulant from transfusion aliquots prior to administration, for example, by centrifugation and volume reduction or washing.

Red Blood Cells are capable of transmitting cytomegalovirus, mediating graft-versus-host disease and causing febrile, nonhemolytic reactions. For recipients at particular risk from these transfusion-related complications, use of CMV reduced-risk (i.e. CMV seronegative or LR-RBC), gamma-irradiated and leukoreduced preparations should be considered.

Dosing:

A dose of one unit of compatible Red Blood Cells will increase the hemoglobin level in an average sized adult who is not bleeding or hemolyzing by approximately 1 g/dL or Hct by 3%. In neonates, a dose of 10-15 mL/kg is generally given, and AS-1 or AS-3 packed red cells with a hematocrit of approximately 60% will increase the hemoglobin by about 3 g/dL.

Response:

Unless the recipient is bleeding or hemolyzing, and provided the transfused red cells are compatible, the post-transfusion hemoglobin can be accurately predicted from the patient's estimated blood volume, baseline red cell volume (=blood volume X venous

hematocrit X 0.91) and transfusion volume.

Transfused red cells have a half-life of approximately 30 days in the absence of other processes that would result in red cell loss or premature removal.

Ref. 27

Indications and Contra-indications:

Red blood cells are indicated for patients with a symptomatic deficiency of oxygen-carrying capacity or tissue hypoxia due to an inadequate circulating red cell mass. They are also indicated for exchange transfusion (e.g., for hemolytic disease of the newborn) and red cell exchange (e.g., for acute chest syndrome in sickle cell disease).

Patients must be evaluated individually to determine the proper transfusion therapy, taking care to avoid inappropriate over- or under- transfusion. Transfusion decisions should be based on clinical assessment and not on laboratory values alone.

Red blood cells should not be used to treat anemia that can be corrected with a non-transfusion therapy (e.g. iron therapy). They also should not be used as a source of blood volume, or oncotic pressure or to improve wound healing, or sense of well being.

For complete Side Effects and Hazards see appendix.

Perioperative/Periprocedural:

General:

The function of a RBC transfusion is to augment oxygen delivery to tissues. Hemoglobin levels during active bleeding are imprecise measures of tissue oxygenation. Adequate or inadequate fluid resuscitation can significantly alter the measured hemoglobin concentration. In addition, a number of factors must be considered besides the blood hemoglobin level such as oxygenation in the lungs, blood flow, hemoglobin-oxygen affinity and tissue demands for oxygen.

Consequently, the adequacy of oxygen delivery must be assessed in individual patients, particularly in patients with limited cardiac reserve or significant atherosclerotic vascular disease. If available, mixed venous O_2 levels, O_2 extraction ratios, or changes in oxygen consumption may be helpful in assessing tissue oxygenation. Other factors to consider, in addition to the above, include anticipated degree and rate of blood loss and the effect of body temperature or drugs/anesthetics on oxygen consumption. Notwithstanding the above, the following recommendations are made by an American Society of Anesthesiologists Task Force:

1. Transfusion is rarely indicated when the hemoglobin level is above 10 g/dL and is almost always indicated in patients when the hemoglobin level is below 6 g/dL;

2. The determination of transfusion in patients whose hemoglobin level is 6-10 g/dL should be based on any ongoing indication of organ ischemia, the rate and magnitude of any potential or actual bleeding, the patient's intravascular volume status and risk of complications due to inadequate oxygenation.

The use of alternative measures to reduce allogeneic red cell use should be considered, including preoperative autologous donation, intra-operative and post-operative autologous blood recovery, acute normovolemic hemodilution, and operative and pharmacologic

measures that reduce blood loss.

Ref. 7

Critical Care:

General:

The same considerations regarding individualization of red cell transfusions apply to critical care as perioperative patients (see above). The effects of anemia must be separated from those of hypovolemia, although both can impede tissue oxygen delivery. Blood loss of greater than 30% of blood volume causes significant clinical symptoms but resuscitation with crystalloid alone is usually successful in young healthy patients with blood loss of up to 40% of blood volume (e.g., 2- liter blood loss in an average adult male). Beyond that level of acute blood loss after adequate volume resuscitation, acute normovolemic anemia will exist. However, oxygen delivery in healthy adults is maintained even with hemoglobin levels as low as 6-7 g/dL. Thus up to 40% of the blood volume in a bleeding, otherwise healthy young adult can be replaced with crystalloid without the need for red cell transfusion.

In support of a conservative red cell transfusion policy in critical care is a multicenter, randomized, controlled trial comparing a transfusion trigger of 7 g/dL with a trigger of 9 g/dL in normovolemic critically ill patients. Overall 30-day mortality was similar in the two groups and in the subset of more seriously ill patients. However, in less acutely ill or younger patients, the restrictive strategy resulted in lower 30-day mortality.

In support of considering cardiovascular status in the decision to transfuse red cells is a retrospective study of transfusion in elderly patients with acute myocardial infarction which showed lower short-term mortality when patients were transfused with a hemoglobin as high as 10 g/dL.

Thus, transfusion triggers for red cells in critical care

must be customized to defined patient groups, and the decision to transfuse must be made on the basis of individual patient characteristics. Unfortunately, the availability of carefully performed clinical trials to assist the clinician is extremely limited.

Ref. 24, 62

Neonates:

Neonates and Critically Ill Children:

Infants may require simple or exchange transfusions for hemolytic disease of the newborn (HDN) or symptomatic anemia in the first months of life.

The American Academy of Pediatrics has published guidance on specific indications for exchange transfusion for newborn infants 35 or more weeks of gestation with hyperbilirubinemia, including that caused by HDN. Infants with jaundice caused by HDN are at greater risk of bilirubin encephalopathy and are treated more intensively than infants with "physiologic" jaundice at any given serum unconjugated bilirubin concentration.

Ref. 3

Apart from HDN, neonatal anemia occurs in many preterm infants because of iatrogenic blood loss for laboratory tests, concurrent infection or illness and inadequate hematopoiesis in the first weeks of life. Transfusion thresholds for preterm infants and critically ill children have been widely debated for years, but recent randomized studies support the use of a restrictive strategy (e.g. transfusion at lower hemoglobin thresholds) compared to more liberal criteria (e.g. transfusion at higher hemoglobin thresholds).

In the multicenter PINT (Premature Infants in Need of Transfusion) study, 451 very low birthweight infants were randomly assigned to receive red cell transfusions either by restrictive or liberal criteria. Infants in the restrictive transfusion group had lower mean hemoglobin values than infants in the liberal group, and more infants

avoided transfusion completely in the restrictive group (5%) compared to the liberal group (11%). There was no difference between the two groups in the composite outcome (death, severe retinopathy, bronchopulmonary dysplasia, and brain injury), supporting the use of restrictive transfusion criteria. In a smaller, single-center trial, Bell et al. randomized 100 preterm infants to either restrictive or liberal transfusion criteria, and found a reduction in the number of transfusions in the restrictive group. However, infants in the restrictive group were noted to have more apnea episodes and neurologic events than infants in the liberal group. In conclusion, the documented benefits of restrictive transfusion practice are a decrease in the number of transfusions and exposure to fewer RBC donors, if a limited-donor program is not used. It is possible that the higher hemoglobin values maintained in the liberal transfusion group in the study of Bell et al. compared with the corresponding group in the PINT trial may have decreased the risk of apnea and brain injury.

These two randomized studies suggest that transfusion thresholds can be lower than what are currently followed in most hospitals, but identify the need for additional clinical studies. General guidelines for transfusion must take into consideration the infants' cardiorespiratory status but transfusion decisions must be tailored to the individual patient.

Table: General Guidelines For Small-volume (10-15 mL/kg) Transfusion To Infants:

Maintain HCT between :	Clinical Status
40-45%	Severe cardiopulmonary disease* (e.g., mechanical ventilation >0.35 FiO_2)
30-35%	Moderate cardiopulmonary disease (e.g. less intensive assisted ventilation such as nasal CPAP or supplemental oxygen)
30-35%	Major surgery
20-30%	Stable anemia, especially if unexplained breathing disorder or unexplained poor growth

*Must be defined by institution

Strauss R., ISBT Science Series 2006, 1:11-4, Blackwell Publishing Ltd., reprinted with permission.

Ref. 11, 12, 26, 57

Less controversial are the results from the TRIPICU (Transfusion Requirements in the Pediatric Intensive Care Unit) study, which demonstrated a hemoglobin threshold of 7 g/dL for red-cell blood transfusion is not inferior to a treatment strategy using a hemoglobin threshold of 9.5 g/dL among critically ill but stable children being treated in ICUs. A higher threshold may be indicated for patients with cardiovascular disease or children with severe hypoxemia, hemodynamic instability, active blood loss or cyanotic heart disease.

Ref. 17, 28, 57

Hematology/Oncology:

Asymptomatic Chronic Anemia:
Treat with pharmacologic agents based on the specific diagnosis (e.g., Vit B12, folic acid, recombinant erythropoietin, iron).

Symptomatic Chronic Anemia:
Transfuse to minimize symptoms and risks associated with anemia. Transfusion is usually required when hemoglobin is at 6 g/dL.

Severe Thalassemia:
Transfuse to help prevent symptomatic anemia and suppress endogenous erythropoiesis by maintaining hemoglobin at 9.5-10.5 g/dL.

Sickle Cell Disease:
Evidence-based clinical guidelines and consensus statements have outlined indications for transfusion in sickle cell disease. SCD patients should be transfused with leukocyte-poor, antigen-matched blood to reduce the frequency of transfusion reactions and the development of antibodies. The choice between simple transfusion as opposed to exchange transfusion is often based on clinical judgment and available resources, with few clinical studies to guide decisions. In preparation for surgery requiring general anesthesia, however, simple transfusion to increase hemoglobin to 10 g/dL was as effective as exchange transfusion in preventing perioperative complications in patients with sickle cell anemia and was associated with less blood usage and a lower rate of red cell alloimmunization.

Chronic transfusion therapy to maintain the HbS below 30% of the total hemoglobin prevents first stroke in high-risk children with abnormal transcranial Doppler studies and prevents recurrent stroke in those with a history of infarctive stroke. The treatment goal for prevention of recurrent stroke may be relaxed to less than 50% HbS after several complication-free years, but treatment

cannot be safely discontinued at any point. Similarly, prophylactic transfusion cannot be safely discontinued in children with sickle cell anemia who have abnormalities on transcranial Doppler studies at high risk of stroke (STOP 2). In contrast to simple transfusion, exchange transfusion can prevent iron accumulation and may reverse iron overload in chronically transfused patients.

Accepted Indications for Transfusion in Sickle Cell Disease:

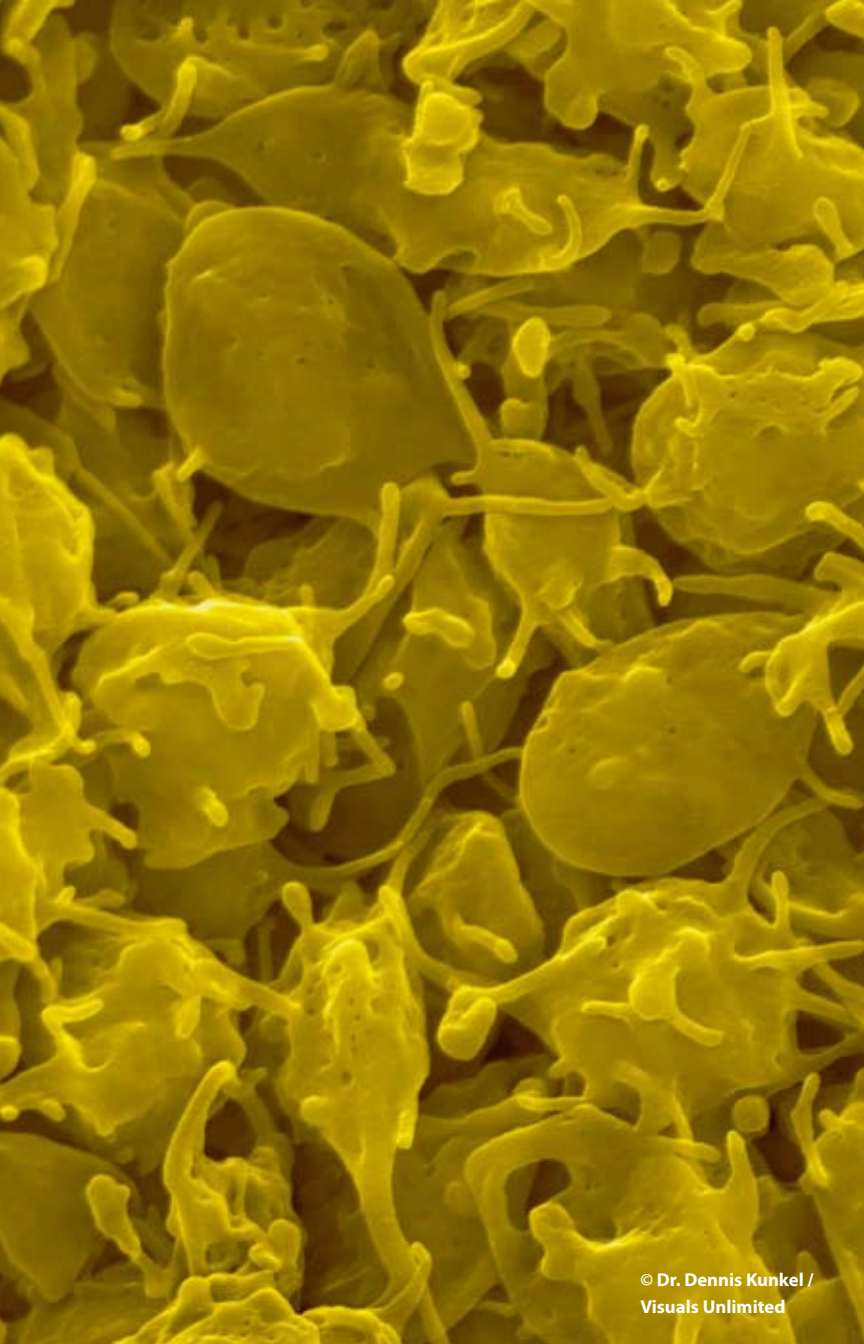
Episodic or Acute Complications of SCD	Chronic Complications of SCD
• Severe anemia	• Prevention of stroke in children with abnormal transcranial Doppler studies*
• Acute splenic sequestration	• Prevention of stroke recurrence*
• Transient red cell aplasia	• Chronic debilitating pain
• Preparation for general anesthesia	• Pulmonary hypertension
• Sudden severe illness*	• Anemia associated with chronic renal failure
• Acute chest syndrome*	
• Stroke*	
• Acute multiorgan failure*	

*Managed with simple transfusion or erythrocytapheresis

Ref. 2, 25, 30, 34, 59, 60

Controversial indications:
Priapism
Leg ulcers
Pregnancy
Preparation for infusion of contrast media
"Silent" cerebral infarct and/or neurocognitive damage

Inappropriate Indications and Contraindications:
- Chronic, steady-state (asymptomatic anemia)
- Uncomplicated pain episodes
- Infection
- Minor surgery that does not require general anesthesia
- Aseptic necrosis of the hip or shoulder (unless indicated for surgery)
- Uncomplicated pregnancy



PLATELETS | GENERAL INFORMATION

Components:

Approved names: Platelets; Platelets Pooled; Platelets Pheresis.

Platelets are also referred to as whole blood derived platelets, random donor platelets, randoms, platelet concentrates, or RDPs. Platelets Pheresis are also referred to as single donor platelets, or SDPs.

Preparation variations include Platelets pre-storage pooled, Platelets Irradiated; Platelets Pooled Irradiated; Platelets Pheresis Irradiated; Platelets Leukocytes Reduced; Platelets Pheresis Leukocytes Reduced; and Platelets Pheresis, Leukocytes Reduced, Irradiated.

Description of Components:

Platelets (RDP): derived from Whole Blood; should contain $\geq 5.5 \times 10^{10}$ platelets (average content approximately 8.0×10^{10}) per bag in approximately 50 mL of plasma. Anticoagulant is the same as used for the whole blood collection, usually CPD or CP2D. Prestorage pooled platelets should contain ($\geq 5.5 \times 10^{10}$) x number of RDP in the pool.

Platelets Pheresis (SDP): obtained using automated instrumentation; should contain $\geq 3.0 \times 10^{11}$ platelets (average content approximately $3.5\text{-}4.0 \times 10^{11}$) per bag in about 250 mL of plasma. Anticoagulant is ACD.

Selections and Preparations:

Four to ten RDPs are pooled at the blood center (prestorage pooled platelets) or the hospital prior to transfusion to prepare an adult dose. SDPs are ready for transfusion.

SDPs and RDPs should be ABO-identical with the recipient when possible.

Rh-negative recipients should receive Rh-negative platelets when possible, particularly in women of childbearing potential. Consider administering Rh immune globulin if Rh-positive platelets need to be administered.

Patients at risk for transfusion-associated graft-versus host disease (TA-GVHD) should received gamma-irradiated platelets.

Dosing:

Four to ten units of pooled RDPs or one SDP for thrombocytopenia or thrombocytopathy meeting pre-specified triggers.

To help prevent or treat bleeding, transfuse as needed to maintain target platelet count.

Response:

Measure platelet count from 10 minutes to 3 hours after transfusion. Generally, expect an adult platelet count increment of approximately 7-10,000/ mm^3 for each RDP given, or 30-60,000/ mm^3 for each SDP given. In neonates and infants, a dose of 5-10 mL/kg of platelets (RDP or SDP) should result in a 50-100,000/mm^3 increment.

At least 7.1 x 10^9 platelets/L are consumed daily in endothelial support functions, the equivalent of approximately one RDP daily for a 70 kg adult with marrow failure.

Response to platelet transfusion is adversely affected by the presence of fever, sepsis, splenomegaly, severe bleeding, consumptive coagulopathy, HLA alloimmunization and treatment with certain drugs (e.g., amphotericin B).

Ref. 9, 41, 50, 51

Indications and Contra-indications:

Use to treat bleeding due to critically decreased circulating platelet counts or functionally abnormal platelets.

Use prophylactically to prevent bleeding at pre-specified low platelet counts. In general, maintain platelet count >10,000/mm^3 in stable, non-bleeding patients, >20,000/mm^3 in unstable non-bleeding patients and >50,000/mm^3 in patients undergoing invasive procedures or actively bleeding.

Do not use in patients with autoimmune thrombocytopenia or thrombotic thrombocytopenic purpura except for life-threatening hemorrhage.

For complete Side Effects and Hazards see appendix.

Ref. 19

Perioperative/Periprocedural

Cardiothoracic Surgery:

a) Routine prophylactic transfusions are not required in the absence of bleeding.
b) When coagulation parameters are not significantly abnormal, counts <100,000/mm^3 accompanied by major unexpected microvascular bleeding are appropriately treated with platelet transfusion.

Other Surgical Procedures:

a) Intraoperative platelet counts should be obtained to guide transfusion. Microvascular bleeding in the setting of potential dilutional thrombocytopenia may require empiric transfusion before counts are available.
b) Prophylactic preoperative transfusion is rarely required for counts >100,000/mm^3, is usually required for counts <50,000/mm^3 and is guided by risk factors for intermediate counts.
c) Procedures with insignificant blood loss or vaginal deliveries can be performed at counts <50,000/mm^3 without prophylactic transfusion.
d) Neurologic or ophthalmologic procedures require a platelet count near 100,000/mm^3.
e) Transfusion may be required with apparently adequate counts when known or suspected platelet dysfunction results in microvascular bleeding.

Specific Procedures:

a) When prophylactic transfusion is deemed necessary, a post-transfusion count should be obtained to assure an appropriate increment before performance of the procedure.
b) In the absence of other coagulopathy, major invasive procedures require platelet counts of at least 40,000 to 50,000/mm^3 (including CVP placement, paracentesis / thoracentesis, respiratory tract / GI biopsies, closed liver biopsy, lumbar puncture, sinus aspiration & dental

extraction).
c) A threshold of 80,000/mm^3 has been proposed for spinal epidural anesthesia.
d) Fiberoptic bronchoscopy without biopsy by an experienced operator may be safely performed in the presence of a platelet count <20,000/mm^3.
e) GI endoscopy without biopsy may be safely performed at platelet counts <20,000/mm^3.

Platelet Function Defects:

Patients with congenital or acquired defects in platelet function may be transfused for critical bleeding or before major surgery regardless of the platelet count. Transfusion is generally not indicated when platelet dysfunction is extrinsic to the platelet (e.g., uremia, certain types of von Willebrand Disease, hyperglobulinemia) since transfused platelets function no better than the patient's own platelets. When platelet surface glycoproteins are missing (e.g., Glanzmann Thrombasthenia, Bernard-Soulier Syndrome), transfusion should be undertaken only when more conservative efforts to manage bleeding fail since alloimmunization may cause future life-threatening refractoriness.

Antiplatelet Agents:

Thienopyridine platelet ADP receptor inhibitors and direct glycoprotein IIb/IIIa inhibitors impair platelet function. Platelets should not be transfused prophylactically without thrombocytopenia, but high dose therapeutic transfusion may be required for life-threatening hemorrhage in patients on these drugs.

Neonates:

Neonates undergoing invasive procedures / minor surgery or experiencing clinically significant bleeding may be transfused at <50,000/mm^3. For major surgery or bleeding in the face of additional hemostatic stressors (e.g., disseminated intravascular coagulation, necrotizing

enterocolitis) transfusion is appropriate at counts <100,000/mm^3.

Ref. 4, 5, 7, 9, 20, 29, 42

Critical Care:

Massive Transfusion:

A transfusion target of >50,000/mm^3 is recommended for acutely bleeding patients and >100,000/mm^3 for those with multiple trauma or CNS injury. The platelet count may fall below 50,000/mm^3 when >1.5–2 blood volumes have been replaced with red cells. In the presence of microvascular bleeding, transfusion may be appropriate when counts are known or suspected to be <100,000/mm^3.

Disseminated/Local Intravascular Coagulation (DIC/LIC) and/or Sepsis:

Microvascular bleeding is treated in children and adults with platelet counts <50,000/mm^3 or neonates <100,000/mm^3.

Neonates:

A prophylactic transfusion trigger of <20,000/mm^3 for stable neonates at term, or <30,000/mm^3 for stable premature neonates, is justified. High-risk neonates (those with extremely low birthweight, perinatal asphyxia, sepsis, ventilatory assistance with an FIO_2>40% or clinical instability) may be transfused at <30,000/mm^3 at term or <50,000/mm^3 if premature.

Infants on extracorporeal membrane oxygenators (ECMO) are usually transfused to maintain a platelet count >100,000/mm^3.

Ref. 7, 8, 14, 29, 40, 43, 46, 55

Hematology/Oncology:

Acute Leukemia and Following High Dose Chemotherapy:

A prophylactic transfusion trigger of ≤10,000/mm^3 may be used for stable patients, except as noted below. Patient-specific clinical data may increase the threshold at which prophylactic transfusion is desirable (e.g., major/minor bleeding, coagulopathy, drug-induced platelet dysfunction, fever/sepsis, hyperleukocytosis, planned procedures, use of antithymocyte globulin, serious mucositis or cystitis, acute graft-versus-host disease, liver dysfunction/veno-occlusive disease or rapid decline in counts). Prophylactic platelets may also be given at higher counts when availability of compatible platelet products is reduced (e.g., short-dated matched units).

Higher-than-usual doses of platelets result in longer intervals between transfusions which may be of value in the outpatient setting.

Therapeutic transfusion for major bleeding should maintain counts ≥50,000/mm^3.

Chemotherapy for Solid Tumors:

The usual prophylactic transfusion trigger is ≤10,000/mm^3. The greater risk of bleeding from bladder neoplasms / necrotic tumors and the serious impact of even minor bleeding in patients with limited physiologic reserve may warrant a transfusion trigger of ≤20,000/mm^3.

Transfusion Refractoriness:

a) Post-transfusion platelet counts obtained 10-60 minutes after infusion should be obtained whenever possible. The 10-60 minute post infusion count measures transfusion recovery which is most sensitive to immune platelet destruction. Post-infusion counts at 24 hours assess platelet survival, which is more sensitive to non-immune factors such

as sepsis, splenomegaly, DIC, etc. The American Society of Clinical Oncology recommends that additional products be given if post transfusion counts are unacceptable.

b) Alloimmune refractoriness is more likely in the setting of at least two consecutive poor platelet increments at 10-60 minutes after transfusion. Alloimmunization should be confirmed by demonstration of antibodies to platelets (e.g., to human leukocyte antigens [HLA] or human platelet antigens [HPA]). Single donor products identified by HLA/HPA matching and/or crossmatching should be transfused. In the absence of HLA/HPA-compatible products, fresh ABO-compatible units are preferred.

c) The incidence of HLA alloimmunization has been shown to be reduced by the use of leukoreduced blood products (platelets and RBCs) in any patient expected to receive multiple platelet transfusions during the course of therapy.

d) Severely alloimmunized patients who do not respond to available matched products do not benefit from unmatched prophylactic platelet transfusions and should only be transfused for active bleeding.

Idiopathic Thrombocytopenic Purpura (ITP):

a) Patients who experience major, life-threatening bleeding or intraoperative hemorrhage should receive high-dose platelet transfusions.

b) Prophylactic transfusions are usually inappropriate since transfused platelets do not survive any longer than patients' native platelets. Transfusion may be considered before elective splenectomy with platelet counts $\leq 10{,}000/mm^3$.

Thrombotic Thrombocytopenic Purpura (TTP) and Heparin-Induced Thrombocytopenia with Thrombosis (HITT):

Due to the significant risk of fatal thrombosis, platelets

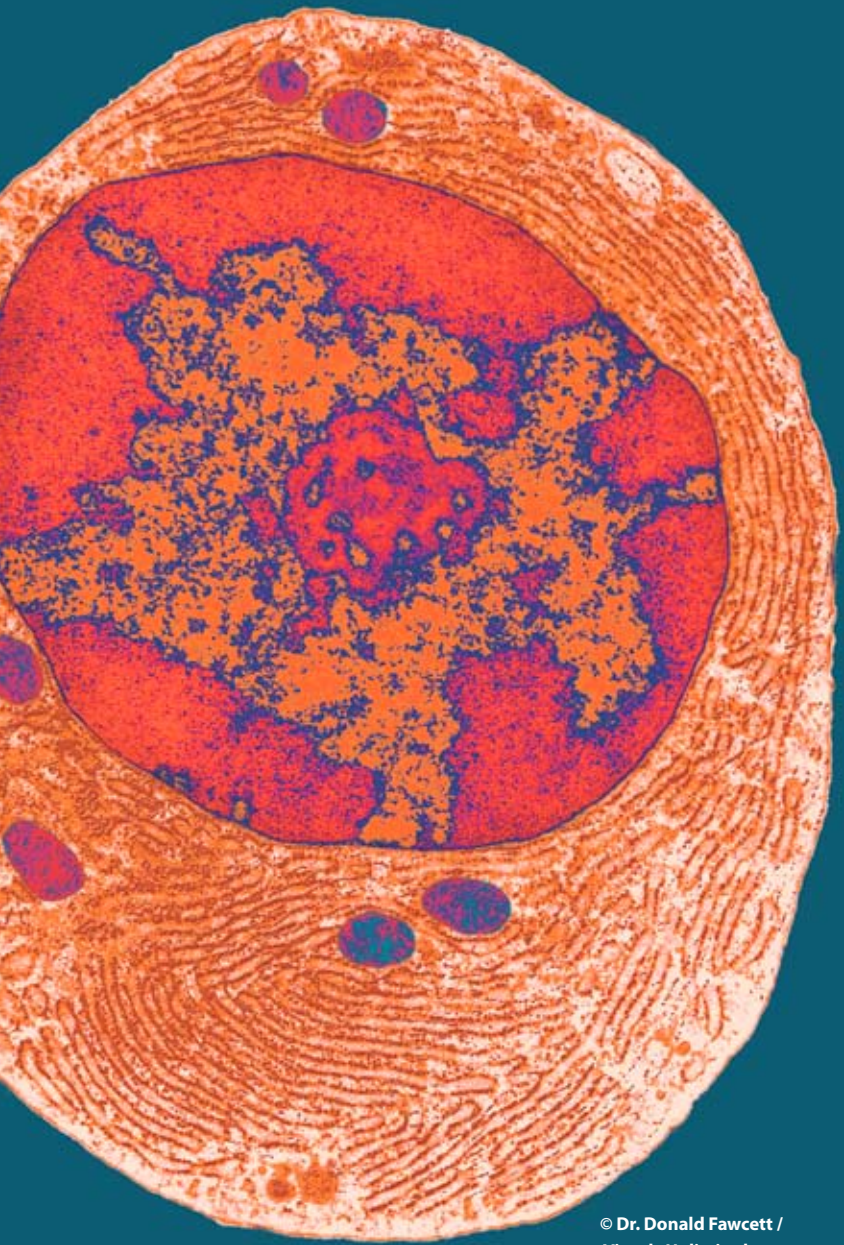
should only be transfused in the setting of life-threatening hemorrhage.

Post-Transfusion Purpura (PTP):
Platelets may be used therapeutically for severe bleeding. Transfusion of randomly selected platelets is usually ineffective. Though efficacy is not well documented, human platelet antigen (HPA)-1a (PI^{A1})-negative platelets are frequently given empirically while specific alloantibody testing is in progress. High-dose intravenous immunoglobulin is the treatment of choice for PTP.

Neonatal Alloimmune Thrombocytopenia (NAIT):
Platelets should lack the HPA recognized by circulating maternal antibodies, although concentrates from random donors may be effective when matched platelets are unavailable. If maternal platelets are used, they should be washed or volume-reduced and irradiated.

Aplastic Anemia:
Transfuse stable patients prophylactically at counts $\leq 5{,}000/mm^3$ and patients with fever or minor hemorrhage at counts $6{,}000\text{-}10{,}000/mm^3$.

Ref. 7, 9, 13, 14, 15, 20, 21, 41, 42, 43, 50



FROZEN PLASMA | GENERAL INFORMATION

Components:

Approved name: Fresh frozen plasma, Fresh frozen plasma donor retested, Plasma frozen within 24 hours after phlebotomy, Plasma cryoprecipitate reduced.

Also referred to as FFP, FP24, plasma or cryo poor plasma.

Preparation variations include:
Thawed Plasma, Liquid Plasma.

Description of Components:

Plasma consists of the noncellular portion of blood that is separated and frozen after donation. It may be prepared from whole blood or collected by apheresis. The anticoagulant solution used and the volume are indicated on the label. The volume of the unit is approximately 250 mL but variation may be expected. FFP is frozen at -18C or colder within 6-8 h of collection (depending upon the anticoagulant) and contains functional quantities of all coagulation factors. Plasma frozen within 24 hours (FP24) and thawed plasma may contain variably reduced levels of Factor V and Factor VIII, Despite these differences, FP24, thawed plasma and FFP are generally used for the same indications.

Plasma, cryoprecipitate reduced contains 20-30% reduced levels of Factor VIII, von Willebrands' factor, fibrinogen, fibronectin and Factor XIII.

By convention, 1 U of a coagulation factor is defined as that activity present in each milliliter of a standard pool of plasma units.

Ref. 15, 35, 37

Selection and Preparation:

Plasma for transfusion must be ABO-compatible with the recipient's red cells, for example, group A Plasma is suitable for group A and group O patients. Group AB Plasma is suitable for all blood types. Frozen Plasma must be thawed, usually in a water bath, and infused immediately or stored at 1-6°C for up to 24 hours. FFP and FP24 may be relabeled as Thawed Plasma and used as a source of stable coagulation factors for up to 5 days, unless it was collected by apheresis in an open collection system. Plasma, cryoprecipitate reduced is indicated in the treatment of Thrombotic Thrombocytopenic Purpura (TTP).

Ref. 19, 35, 37

Dosing:

The dose of plasma is determined by the patient size and clinical condition. When used to correct multiple coagulation factor deficiencies, plasma transfusion should be guided by coagulation testing. A prothrombin time (PT) greater than 1.5 times the mid-range of normal, an activated partial thromboplastin time (APTT) greater than 1.5 times the top of the normal range, or factor assay less than 25%, can be used as thresholds at which therapeutic or prophylactic replacement may be indicated in an appropriate clinical setting. When such testing is not readily available, clinical evidence of bleeding may be used to direct transfusion decisions. Plasma should be administered in doses calculated to achieve a minimum of 30% of plasma factor concentration. This is usually achieved with the administration of 10-20 mL/kg, though more may be required depending upon the clinical situation.

When used to correct isolated coagulation factor deficiencies for which no concentrated preparation is available (e.g., factor V, or XI), dosing will depend on the half-life of the specific factor, the pretransfusion

level of the factor, the desired post transfusion level and the duration of raised levels required.

Ref. 7, 18, 38

TTP initially requires exchange of 1 – 1.5 plasma volume daily and may need to be increased to twice-daily single plasma volume exchanges in refractory patients. The volume and/or frequency of exchange may be tapered as disease activity declines.

Response:

Frozen Plasma used to correct coagulation abnormalities should stop bleeding and bring the APTT and PT within the hemostatic range, but transfusion will not always correct these values, or the correction may be transient.

Frozen Plasma used to treat TTP should result in an increasing platelet count associated with a decrease in serum lactate dehydrogenase.

Indications and Contra-indications:

Frozen Plasma is indicated for use in patients with the following conditions:

1. Active bleeding due to deficiency of multiple coagulation factors, or risk of bleeding due to deficiency of multiple coagulation factors.
2. Severe bleeding due to warfarin therapy, or urgent reversal of warfarin effect
3. Massive transfusion with coagulopathic bleeding.
4. Bleeding or prophylaxis of bleeding for a known single coagulation factor deficiency for which no concentrate is available.
5. Thrombotic thrombocytopenic purpura.
6. Rare specific plasma protein deficiencies, such as C1-inhibitor.

Frozen Plasma should not be used for

1. Increasing blood volume or albumin concentration
2. Coagulopathy that can be corrected with administration of Vitamin K.
3. Normalizing abnormal coagulation screen results, in the absence of bleeding.

For complete Side Effects and Hazards see appendix.

Ref. 1, 7, 15

Perioperative:

Warfarin and Liver Disease:
Frozen Plasma may be used to treat multiple coagulation factors (e.g., liver disease) prior to an invasive procedure that would create a risk of bleeding. However, the response may be unpredictable and complete normalization of the hemostatic defect does not occur. Patients with liver disease or those taking warfarin may safely undergo operative or invasive procedures when the PT is ≤1.5 times mid-range normal.

Frozen Plasma is indicated for patients on warfarin only if there is serious bleeding or urgent reversal of warfarin effect is necessary. Other patients can be treated simply with withdrawal of warfarin and administration of vitamin K.

Factor Deficiency:
Prophylactic correction of a known factor deficiency for which specific concentrates are unavailable is guided by recommended perioperative hemostatic levels for each type of procedure.

Massive Transfusion and Cardiopulmonary Bypass:
Frozen Plasma may be used to treat excessive microvascular bleeding, as determined on visual assessment of the operative field jointly by the anesthesiologist and surgeon when the coagulation screening test results are abnormal or not available in a timely fashion. However, microvascular bleeding may be a result of hypofibrinogenemia or residual heparin effect.

Ref. 7, 18, 38, 47

Oncology: See Critical Care

Critical Care:

Warfarin:

Patients on warfarin who experience serious bleeding are treated with Vitamin K (at a dose determined by the INR) and Frozen Plasma or prothrombin complex concentrates as clinically warranted.

Acute Disseminated Intravascular Coagulation:

Addressing the underlying cause is the foundation of treatment, and the patient is supported with transfusion of Frozen Plasma in combination with Platelets and Cryoprecipitate. If there is no bleeding, blood products are not indicated prophylactically, regardless of the results of laboratory tests.

Thrombotic Thrombocytopenic Purpura:

If plasma exchange is not immediately available, simple transfusion of plasma can be a useful alternative until exchange can be started.

Ref. 7, 18, 38

Hematology:

Specific Plasma Protein Deficiencies:
Deficiencies of other isolated plasma proteins and factors in a setting where concentrates are not readily available are also treated with Frozen Plasma:

a) Treatment or prophylaxis of thromboembolism in antithrombin, protein C and protein S deficiencies.
b) Heparin resistance (antithrombin III deficiency) in a patient requiring heparin
c) Therapy of acute angioedema or preoperative prophylaxis in hereditary C1-inhibitor deficiency.

Ref. 7, 18, 38

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OGEN

Components:

Approved names: Cryoprecipitated Antihemophilic Factor (AHF); Cryoprecipitated AHF, Pooled.

Also referred to as cryoprecipitate, cryoprecipitate pool, cryo, pooled cryo.

Description of Components:

A cryoprecipitate unit is prepared by thawing one unit of FFP between 1-6°C and recovering the cold insoluble precipitate. The cryoprecipitate is refrozen within 1 hour.

If the label indicates "Cryoprecipitated AHF, Pooled," several units of cryoprecipitate have been pooled into one bag, and the volume of the pool is indicated on the label.

Cryoprecipitate contains concentrated levels of fibrinogen, Factor VIII:C, Factor VIII:vWF (von Willebrand factor), Factor XIII, and fibronectin.

Each unit of cryoprecipitate should contain at least 80 IU Factor VIII:C and 150 mg of fibrinogen in 5-20mL of plasma.

Selection and Preparation:

Cryoprecipitate is considered to be an acellular blood component. Compatibility testing is unnecessary. Rh type need not be considered. It is preferable to use cryoprecipitate that is ABO-compatible with the recipient's red cells.

CMV testing and leukoreduction are not required. Frozen cryoprecipitate is thawed in a protective plastic overwrap in a waterbath at 30-37°C up to 15 minutes. Thawed cryoprecipitate should be kept at room temperature and transfused as soon as possible after thawing or within 6 hours if it is a closed single unit or has been pooled prior to freezing. It should be transfused within 4 hours if it is

an open system or units have been pooled after thawing.

For pooling, the precipitate in each unit should be mixed well with 10 –15 mL of diluent (0.9% Sodium Choride, Injection USP) to ensure complete removal of all material from the container. Cryoprecipitate pooled prior to freezing requires no extra diluent.

Dosing:

The number of cryoprecipitate units can be estimated by using the following calculation

- Weight (Kg) x 70mL/Kg = blood volume (mL)
- Blood volume (mL) x (1.0-hematocrit) = plasma volume(mL)
- fibrinogen required (mg) = (desired fibrinogen level (mg/dL) - initial fibrinogen level (mg/dL)) multiplied by (plasma volume (mL) divided by 100).
- Bags of cryo required = mg fibrinogen required divided by 250 mg fibrinogen per bag of cryo.

The frequency of dosing depends on the half-life and recovery of the coagulation factor that is being replaced (check factor levels).

A typical dose for the treatment of hypofibrinogenemia is one cryoprecipitate unit per 7 - 10 kg of body weight.

Ref. 15

Response:

Pretransfusion and posttransfusion coagulation factor levels should be determined to assess the adequacy of the cryoprecipitate dose.

One unit of cryoprecipitate per 10 kg of body weight raises plasma fibrinogen concentration by ~ 50 mg/dL in the absence of continued consumption or massive bleeding (assuming minimum fibrinogen content per bag of cryo).

Indications and Contra-indications

Cryoprecipitate is indicated for bleeding associated with fibrinogen deficiencies and Factor XIII deficiency.

Patients with hemophilia A or von Willebrand's disease (vWD) should only be treated with cryoprecipitate when appropriate Factor VIII concentrates or Factor VIII concentrates containing FVIII: vWF are not available.

Do not transfuse cryoprecipitate unless laboratory studies confirm deficiency of a specific clotting protein for which this component is indicated (e.g. fibrinogen).

For complete Side Effects and Hazards see appendix.

Ref. 15

Perioperative:

Fibrin Sealant:
Both autologous and allogeneic cryoprecipitate units have been used in the preparation of fibrin sealant for topical use, but commercially produced, viral inactivated fibrin sealant is preferable with respect to safety and efficacy.

Ref. 58

Oncology:

Hypofibrinogenemia / dysfibrinogenemia:
Transfuse for bleeding associated with fibrinogen levels <100 to 120 mg/dL or reduced functional levels of fibrinogen.

Ref. 22

Critical Care

Cryoprecipitate is especially useful when it is not possible to give enough FFP to provide adequate levels of fibrinogen without volume overloading the patient.

Cryoprecipitate has been used for uremic bleeding, but efficacy has not been clearly demonstrated, and 1-deamino-8-D-arginine vasopressin (DDAVP) and other modalities are preferred.

Cryoprecipitate should not be used in the critical care setting as a source of fibronectin to improve reticuloendothelial system function.

Massive Transfusion:
Transfuse for bleeding in massively transfused patients when the fibrinogen level is documented to be <100 mg/dL. This not likely to occur until after ~1 1/2 blood volumes are replaced.

Hypofibrinogenemia / dysfibrinogenemia:
Transfuse for bleeding. Most cases of hypofibrinogenemia/ dysfibrinogenemia in critical care

are associated with DIC or hepatic insufficiency.

Ref. 31

Hematology

Congenital fibrinogen deficiencies are uncommon, and are variably associated with bleeding. The treatment of patients with an isolated fibrinogen deficiency should be reserved for episodes of clinical bleeding, or when there is a significant risk of bleeding complications due to an invasive procedure or pregnancy.

For hemophilia A or vWD, cryoprecipitate should only be used if appropriate recombinant or virus- inactivated Factor VIII or Factor VIII:vWF concentrates are not available. DDAVP is the treatment of choice for type 1 vWD.

Congenital afibrinogenemia / Congenital and acquired dysfibrinogenemia:
Transfuse for bleeding or risk of bleeding associated with a fibrinogen level <100 mg/dL by a quantitative or functional assay.

Factor XIII deficiency (Rare):

a) Transfuse for bleeding and prophylaxis.
b) Factor XIII deficiency is rare, and characterized by bleeding and poor wound healing.
c) Factor XIII has a half-life of 4 to 14 days, and only ~ 1-5% activity levels are needed to control bleeding. Newborns with Factor XIII deficiency should be placed on a prophylactic regimen of replacement therapy because of the high incidence of intracranial hemorrhage.
d) Virus inactivated Factor XIII concentrates are preferred for the treatment of Factor XIII deficient patients, but are not readily available. Cryoprecipitate can be given in doses of one bag per 10-20 kg of body weight every 3 to 4 weeks. FFP can also be used.

Ref. 4, 8, 15, 31

ROLE OF THE HOSPITAL TRANSFUSION COMMITTEE

Description:

Hospitals are required by accrediting and regulatory agencies (e.g., Joint Commission, AABB and College of American Pathologists) to ensure appropriate use of blood products. The Code of Federal Regulations (CFR) requires a hospital to develop, implement, and maintain an effective, ongoing, hospital-wide, data-driven quality assessment and performance improvement program. A hospital's transfusion practices should fall under such a program. How this is accomplished may vary from hospital to hospital. Some maintain a Transfusion Committee dedicated solely to this function. Others may charge a Quality Assurance Committee or a Blood and Tissue Committee with this task. For the most part, the accrediting and regulatory agencies do not specify how this peer review function is accomplished, as long as it is being performed.

The responsible committee should address through review or audit the following aspects of blood utilization (list may not be all inclusive):

01. Blood ordering practices
02. Blood refusal practices
03. Patient identification
04. Sample collection and labeling
05. Pretransfusion testing orders
06. Distribution, handling and dispensing
07. Blood administration policies
08. Infectious and non-infectious adverse events
09. Monitoring of patients for appropriate responses
10. Medical errors, near misses and sentinel events
11. Appropriate utilization
12. Wastage and discard rates
13. Ability of transfusion services to meet patient needs
14. Clinical alternatives to blood transfusion (perioperative salvage)

Membership and Structure:

This multidisciplinary committee should include representatives from the Medical Staff (surgery, anesthesia, medicine, hematology, pediatrics), Nursing, Hospital Administration, the Transfusion Service and other interested parties as applicable. Confidentiality rules apply. If guests are invited, they may be excused during discussions with potential liability issues. The Medical Director of the Transfusion Service is a vital member of the committee who may or may not serve as chairperson. The chairperson should, however, be a physician knowledgeable in transfusion medicine.

The committee should establish guidelines for administration of each of the blood components transfused in the institution, using current medical literature as a resource.

The transfusion guidelines should be approved by the Medical Staff prior to implementation. Transfusion guidelines are intended to remind ordering physicians of the transfusion practices for which there is general support and clinical trial evidence. Guidelines cannot be expected to cover every instance in which a transfusion is indicated. In every case, however, the rationale for transfusion should be clearly documented in the medical record.

Process:

The review of transfusions can be done prospectively by transfusion service personnel (before blood is issued) or retrospectively by the Transfusion Committee (after blood is issued) for certain high cost blood products, prospective review may be appropriate to prevent unnecessary transfusions. Similarly, prospective review of potentially inappropriate orders, for example, an order for platelet transfusion to a patient with thrombotic thrombocytopenic purpura or an order for four units of red blood cells for a child, may also require review prior to blood issue. For most transfusions and blood products,

however, involving large numbers of transfusions and patients, retrospective reviews are adequate and most commonly used.

For each transfusion, the following information should be documented:
1. Physician order
2. Indication for transfusion
3. Informed patient consent
4. Patient identification checks
5. Blood component issuance documentation
6. Patient monitoring during transfusion
7. Assessment of patient outcome
8. Applicable lab or clinical results before and after transfusion

Trained hospital quality assurance or compliance staff can do chart or electronic record reviews, using the approved transfusion guidelines developed by the committee. When there are questions about the indications and results of a transfusion, the clinical records should be peer reviewed or reviewed at the transfusion committee meeting.

If the transfusion committee is unable to determine a justification for the transfusion, the patient's physician should be contacted for additional information. If the additional information does not justify the transfusion; there is an opportunity to educate the patient's physician. If the letter is ignored or if repeated unjustified transfusion practices are noted, a department chair or credentialing committee may need to be involved in the review process.

Monitors:

Blood usage should be monitored by whichever parameters are most useful for the institution: by physician, by clinical department, by diagnosis (Diagnosis-Related Groups), or by surgical procedures In addition, the Transfusion Committee must ensure that blood is administered correctly. Before a transfusion

is given there must be informed consent according to the institutional procedures, confirmation that the component is intended for the patient and is not expired, and verification of the patient's identity.

The wastage of all blood components, both allogeneic and autologous, should be monitored. The committee should review adverse reactions to blood products. The committee must also ensure that a mechanism exists for reporting and evaluation of suspected transfusion-transmitted diseases.

Reports:

The Transfusion Committee or its equivalent, should document activities by minutes and generate reports of its work for submission to other entities of the hospital (e.g., clinical departments of the Medical Staff, the Medical Staff Executive Committee, the Clinical Practices Committee, the Credentials Committee). The intent of this reporting is to provide other peer review committees with the results of reviews of transfusion related patient care. These minutes can be protected from inappropriate legal discovery as a critical component of an institutions quality monitoring program.

Summary:

Hospitals are required to review blood transfusion practices and adverse outcomes. Accrediting and regulatory agencies do not specify how this peer review function is accomplished, as long as it is being performed.

The work of auditing and monitoring blood utilization is not sophisticated. It is simply a matter of having appropriate policies and procedures in place, reviewing and revising them as necessary, and monitoring that they are followed.

Ref. 23, 39, 44, 56

APPENDIX: SIDE EFFECTS AND HAZARDS OF BLOOD TRANSFUSION

The following sections are reproduced from the July 2002 Circular of Information:

A. General

The following side effects and hazards pertain to transfusion of Whole Blood or any component prepared from blood collected from individual donors.

Immunologic Complications, Immediate

1. Hemolytic transfusion reaction, the destruction of transfused red cells, is discussed in detail in the section on red-cell-containing components.

2. *Immune-mediated platelet destruction,* one of the causes of refractoriness to platelet transfusion, is the result of alloantibodies in the recipient to HLA or platelet-specific antigens on transfused platelets. This is described in more detail in the section on Platelets.

3. *Febrile nonhemolytic reaction* is typically manifested by a temperature elevation of ≥ 1 C or 2 F occurring during or shortly after a transfusion and in the absence of any other pyrexic stimulus. This may reflect the action of antibodies against white cells or the action of cytokines, either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may accompany about 1% of transfusions; and they occur more frequently in patients previously alloimmunized by transfusion or pregnancy. No routinely available pre- or posttransfusion tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief. Patients who experience repeated, severe febrile reactions may benefit from receiving leukocyte-reduced components. If these reactions are due to cytokines in the component, prestorage leukocyte reduction may be beneficial.

4. *Allergic* reactions usually occur as urticaria, but may also include wheezing or angioedematous reactions. No laboratory procedures are available to predict or prevent these reactions, which usually respond to antihistamines or, in severe cases, corticosteroids or epinephrine.

5. *Anaphylactoid reactions,* characterized by autonomic dysregulation, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm, are a rare but dangerous complication requiring immediate treatment with corticosteroids and epinephrine. The majority of these reactions have been reported in IgA-deficient patients who have IgA antibodies of the IgE class. Such patients may not have been previously transfused and may develop symptoms after infusion of very small amounts of IgA containing plasma, in any blood component.

6. *Transfusion-related acute lung injury (TRALI)* occurs when acutely increased permeability of the pulmonary microcirculation causes massive leakage of fluids and protein into the alveolar spaces and interstitium, usually within 6 hours of transfusion. In many cases, the occurrence of TRALI is associated with the presence of granulocyte antibodies in the donor or recipient. The specific mechanism of action is not clear. Treatment consists of aggressive respiratory support.

Immunologic Complications, Delayed

1. Delayed hemolytic reaction is described in detail in the section on red-cell-containing components.

2. Alloimmunization to antigens of red cells, white cells, platelets, or plasma proteins may occur unpredictably after transfusion. Primary immunization does not become apparent until days or weeks after the immunizing event, and does not usually cause symptoms or physiologic changes. If components that express the relevant antigen are subsequently transfused, there may be accelerated removal of cellular elements from the circulation and/or systemic symptoms. Clinically significant antibodies to red cell antigens will ordinarily be detected by pretransfusion testing. Alloimmunization to antigens of white cells, platelets, or plasma proteins can only be detected by specialized testing.

3. Posttransfusion purpura (PTP) is a rare syndrome characterized by the development of dramatic, sudden, and self-limiting thrombocytopenia, typically 7-10 days after a blood transfusion, in a patient with a history of sensitization by either pregnancy or transfusion. While the immune specificity may be to a platelet-specific antigen the patient lacks, autologous and allogeneic platelets are destroyed. In a bleeding patient, high dose Immune Globulin

Intravenous (IGIV) may promptly correct the thrombocytopenia.

4. Graft-vs-host disease (GVHD) is a rare but extremely dangerous condition that occurs when viable T lymphocytes in the transfused component engraft in the recipient and react against tissue antigens in the recipient. GVHD can occur if the host does not recognize as foreign and reject the transfused cells, and can follow transfusion of any component that contains even very small numbers of viable T lymphocytes. Severely immunocompromised recipients are at greatest risk (e.g., fetuses receiving intrauterine transfusions, recipients of transplanted marrow or peripheral blood progenitor cells, and selected patients with severe immunodeficiency conditions), but GVHD has been reported in immunologically normal recipients heterozygous for a tissue antigen haplotype for which the donor is homozygous. This is most likely to occur when the transfused component is from a blood relative or has been selected for HLA compatibility. GVHD remains a risk with leukocyte-reduced components because they contain sufficient residual T lymphocytes. Irradiation of the component renders T lymphocytes incapable of proliferation and is presently the only approved means to prevent GVHD.

Nonimmunologic Complications

1. *Transmission of infectious disease* may occur because this product is made from human blood. This may be due to known or unknown agents, such as viruses. This may occur despite careful selection of donors and testing of blood. Donor selection criteria are designed to screen out potential donors with increased risk of infection with HIV, HTLV, hepatitis, and syphilis, as well as other agents These procedures do not totally eliminate the risk of transmitting these agents. Cytomegalovirus (CMV) may, unpredictably, be present in white-cell-containing components from donors previously infected with this virus, which can persist lifelong despite the presence of serum antibodies. Up to 70% of donors may be anti-CMV positive. Transmission of CMV by transfusion may be of concern in low-birthweight (≤1200 grams) premature infants born to CMV seronegative mothers and in certain other categories of immunocompromised individuals, if they are CMV seronegative. For at-risk recipients, the risk of CMV transmission by cellular components can be reduced by transfusing CMV seronegative or leukocyte-reduced components. For other infectious agents, there are no

routinely available tests to predict or prevent disease transmission. All potential blood donors are subjected to stringent screening procedures intended to reduce to a minimum the risk that they will transmit infectious agents. These organisms include Babesia spp., Bartonella spp., Borrelia spp., Brucella spp., the agent of Colorado tick fever, Leishmania spp., Parvovirus spp., plasmodia, rickettsia, Toxoplasma spp., and certain trypanosomes.

2. *Bacterial contamination* occurs rarely but can cause acute, severe, sometimes life-threatening effects. Onset of high fever (≥2 C or ≥3.5 F rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after transfusion should suggest the possibility of bacterial contamination and/or endotoxin reaction. Platelet components stored at room temperature, previously frozen components thawed by immersion in a waterbath, and red cell components stored for several weeks at 1-6 C have been implicated. Both gram-positive and gram-negative organisms have been identified as causing septic reactions. Organisms capable of multiplying at low temperatures and those using citrate as a nutrient are most often associated with red cell contamination. A variety of pathogens, as well as skin contaminants, have been found in platelet concentrates. Endotoxemia in recipients has resulted from multiplication of Yersinia enterocolitica in stored red-cell-containing components. Prompt recognition of a possible septic reaction is essential, with immediate discontinuation of the transfusion and aggressive therapy with broad-spectrum antimicrobials and vasopressor agents, if necessary. In addition to prompt sampling of the patient's blood for cultures at several different temperatures, investigation should include examination of material from the blood container by Gram's stain, and cultures of specimens from the container and the administration set.

3. *Circulatory overload,* leading to pulmonary edema, can occur after transfusion of excessive volumes or at excessively rapid rates. This is a particular risk in the elderly and in patients with chronic severe anemia in whom low red cell mass is associated with high plasma volume. Small transfusion volumes can precipitate symptoms in at-risk patients who already have a positive fluid balance. Pulmonary edema should be promptly and aggressively treated, and infusion of colloid preparations, including plasma components and the suspending plasma in cellular components, reduced to a minimum.

4. Hypothermia carries a risk of cardiac arrhythmia or cardiac arrest. Rapid infusion of large volumes of cold blood can depress body temperature, and the danger is compounded in patients experiencing shock or surgical or anesthetic manipulations that disrupt temperature regulation. A blood warming device should be considered if rapid infusion of blood is needed. Warming must be accomplished using an FDA-cleared warming device so as not to cause hemolysis.

5. Metabolic complications may accompany large volume transfusions, especially in patients with liver or kidney disease.
   a.) Citrate "toxicity" reflects a depression of ionized calcium due to the presence in the circulation of large quantities of citrate anticoagulant. Because citrate is promptly metabolized by the liver, this complication is rare. Patients with severe liver disease or those with circulatory collapse that prevents adequate hepatic blood flow, may have physiologically significant hypocalcemia after rapid, large-volume transfusion. Citrated blood administered rapidly through central intravenous access may reach the heart so rapidly that ventricular arrhythmias occur. Standard measurement of serum calcium does not distinguish ionized from complexed calcium. Ionized calcium testing or EKG monitoring is more helpful in detecting physiologically significant alteration in calcium levels.
   b.) Other metabolic derangements can accompany rapid or large-volume transfusions, especially in patients with pre-existing circulatory or metabolic problems. These include acidosis or alkalosis (deriving from changing concentrations of citric acid and its subsequent conversion to pyruvate and bicarbonate) and hyper- or hypokalemia.

B. Red Blood Cells

Listed below are hazards specifically to components that contain red cells.

1. *Hemolytic transfusion* reaction is the immunologic destruction of transfused red cells, nearly always due to incompatibility of antigen on the transfused cells with antibody in the recipient's circulation. (See 5 for discussion of nonimmunologic hemolysis.) The most common cause of severe, acute hemolytic reactions is transfusion of ABO-incompatible blood, resulting from identification errors occurring at some point(s) in the transfusion process. Serologic

incompatibility undetected during pretransfusion testing is a much less common cause of acute hemolysis. If a hemolytic reaction is suspected, the transfusion must be stopped and the transfusion service laboratory notified. Information identifying the patient, the transfusion component, and associated forms and labels should be reviewed immediately to detect possible errors. A postreaction blood sample, preferably drawn from a site other than the transfusion access, should be sent to the laboratory along with the implicated unit of blood and administration set. Acute hemolytic reactions characteristically begin with an increase in temperature and pulse rate; symptoms may include chills, dyspnea, chest or back pain, abnormal bleeding, or shock. Instability of blood pressure is frequent, the direction and magnitude of change depending upon the phase of the antigen-antibody event and the magnitude of compensatory mechanisms. In anesthetized patients, hypotension and evidence of disseminated intravascular coagulopathy (DIC) may be the first sign of incompatibility. Laboratory findings can include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum bilirubin; in less catastrophic acute hemolytic reactions, a positive direct antiglobulin test (DAT) is commonly found. Treatment includes measures to maintain or correct arterial blood pressure; correct coagulopathy, if present; and promote and maintain urine flow. Rarely, acute hemolytic reactions may not be overtly apparent. Delayed hemolytic reactions occur in previously red-cell-alloimmunized patients in whom antigens on transfused red cells provoke anamnestic production of antibody that reaches a significant circulating level while the transfused cells are still present in the circulation; the usual time frame is 2 to 14 days after transfusion. Signs may include unexplained fever, development of a positive DAT, and unexplained decrease in hemoglobin/hematocrit. Hemoglobinemia and hemoglobinuria are uncommon, but elevation of lactic dehydrogenase (LDH) or bilirubin may be noted. Most delayed hemolytic reactions have a benign course and require no treatment.

2. Antigens on transfused red cells may cause red cell *alloimmunization* of the recipient, who may experience red cell antibody-mediated reactions to subsequent transfusions. There is no practical way to predict or prevent alloimmunization in any specific transfusion recipient. Clinically significant antibodies to red cell antigens will usually be detected in pretransfusion antibody screening tests.

3. *Circulatory overload,* resulting in pulmonary edema, can accompany transfusion of any component at a rate more rapid than the recipient's cardiac output can accommodate. Whole Blood creates more of a risk than Red Blood Cells because the transfused plasma adds volume without increasing oxygen-carrying capacity. Patients with chronic anemia have increased blood volumes and are at increased risk for circulatory overload.

4. *Iron overload* is a long-term complication of repeated red cell transfusions. Each transfusion contributes approximately 250 mg of iron. Patients requiring multiple transfusions for aplastic anemia, thalassemias, or hemoglobinopathies are at far greater risk than patients transfused for hemorrhagic indications, because blood loss is an effective means of iron excretion. Patients with predictably chronic transfusion requirements should be considered for treatment with iron chelating agents.

5. *Nonimmunologic hemolysis* occurs rarely, but can result from:
   a) introduction of hypotonic fluids into the circulation;
   b) effects of drugs co-administered with transfusion;
   c) effects of bacterial toxins;
   d) thermal injury to transfusion components, by either freezing or overheating;
   e) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies; or
   f) if sufficient physical or osmotic stresses develop, for example, if red blood cells are exposed to excessive heat by non-FDA approved warming methods, mixed with hypotonic solutions or transfused under high pressure through small gauge/defective needles.

C. Platelets

Listed below are hazards that apply specifically to components that contain platelets.

1. *Bacterial Contamination:* Platelet products are the most likely among blood components to be contaminated with bacteria. Gram-positive skin flora are the most commonly recovered bacteria from contaminated platelet units. Symptoms may include high fever (≥2.0 C or ≥3.5 F rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after transfusion. Prompt management should include broad-spectrum antibiotic therapy along with cultures of patient sample, suspected

blood component(s), and administration set. Gram's stain of suspected contaminated unit(s) may be helpful.

2. *Platelet Alloimmunization:* Platelets bear a variety of antigens, including HLA and platelet-specific antigens. Patients transfused with platelets often develop HLA antibodies. The patient may become refractory to all but HLA-selected platelets (see "Platelets Pheresis"). When platelets are transfused to a patient with an antibody specific for an expressed antigen, the survival time of the transfused platelets may be markedly shortened. Nonimmune events may also contribute to reduced platelet survival. It is possible to suggest the presence of immune or nonimmune platelet refractoriness by assessing platelet recovery soon after infusion, i.e., 10- to 60-minute postinfusion platelet increment. In immune refractory states secondary to serologic incompatibility, there is poor recovery in the early postinfusion interval. In nonimmune mechanisms (i.e., splenomegaly, sepsis, fever, intravascular devices, and DIC) platelet recovery within 1 hour of infusion may be adequate while longer-term survival (i.e., 24-hour survival) is reduced. Serologic tests can confirm the presence of alloimmunization. Serologic tests may also be helpful in selecting platelets with acceptable survival.

3. *Red Cell Alloimmunization*: Immunization to red cell antigens may occur because of the presence of residual red cells in Platelets. When Platelet units from Rh-positive donors must be given to an Rh-negative female of childbearing potential because of lack of availability of Rh-negative Platelets, prevention of D immunization by use of Rh Immune Globulin should be considered. In some patients, out-of-group Platelets suspended in incompatible plasma that contains anti-A or anti-B may cause a positive DAT and possibly low-grade hemolysis if the recipient's red cells express the corresponding antigen.

D. Fresh Frozen Plasma (FFP)

Antibodies in the plasma may react with the recipient's red cells, causing a positive DAT. In rare instances, TRALI may develop.

E. Cryoprecipitated-AHF

If a large volume of ABO-incompatible cryoprecipitate is used, the recipient may develop a positive DAT and, very rarely, mild hemolysis.

Fatal Transfusion Reactions

When a fatality occurs as a result of a complication of blood or component transfusions, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), should be notified within one FDA business day (telephone: 301-827-6220; e-mail: fatalities2@cber.fda.gov). Within 7 days after the fatality, a written report must be submitted to the Center for Biologics Evaluation and Research (CBER), Director, Office of Compliance and Biologics Quality, ATTN: Fatalities Program Manager (HFM-650), 1401 Rockville Pike, Rockville, MD 20852-1448. A copy of the report should be sent to the collecting facility, if appropriate. Updated information about CBER reporting requirements may be found at: www.fda.gov/cber/transfusion.htm.

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