

# CIRCULAR OF INFORMATION

## FOR THE USE OF HUMAN BLOOD AND BLOOD COMPONENTS

This circular was prepared jointly by the American Association of Blood Banks, America's Blood Centers and the American Red Cross. It has the approval of the Center for Biologics Evaluation and Research, Food and Drug Administration, and is consistent with the use of uniform blood labeling.

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*Federal law prohibits dispensing the blood and blood components described in this circular without a prescription.*

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## Notice to All Users

The *Circular of Information* is considered an extension of blood and component container labels as the space on those labels is limited.

Blood and blood components are biologic products and, in the form of cellular products, living human tissue intended for use in the treatment of patients. Professional judgment based on clinical evaluation determines the selection of components, dosage, rate of administration, and decisions in situations not covered in this general statement.

**WARNING:** *Because whole blood and blood components are made from human blood, they may carry a risk of transmitting infectious agents, eg, viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Careful donor selection and available laboratory tests do not eliminate the hazard.* Also, septic and toxic reactions can result from transfusion of bacterially contaminated blood and components. Such reactions are infrequent, but may be life-threatening. In addition, blood components may contain certain immunizing substances other than those indicated on the label. For example, Platelets may contain red blood cells and white blood cells as well as platelets. Therefore, this *Circular* as a whole or in part cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described blood or blood components when used for their intended purpose. Attention to the specific indications for blood components is needed to prevent inappropriate transfusion.

Because of the risks associated with transfusion, physicians should remain familiar with currently recognized alternatives to transfusion. Autologous transfusion techniques (such as perioperative collection and preoperative donation) should be considered, when indicated, to reduce the risks of disease transmission and immune reactions from allogeneic donations.

This *Circular* is supplied to conform with applicable federal statutes and regulations of the Food and Drug Administration (FDA), US Department of Health and Human Services.

## General Information

### Donors

Blood and components described in this *Circular* have been collected from human donors who have been questioned about acquired immunodeficiency syndrome (AIDS) high-risk behavior and about practices and circumstances that should cause them to refrain from donating; have satisfactorily completed a health assessment that includes a questionnaire on past and present illnesses; have satisfied minimum physiologic criteria; and who may have had the opportunity to confidentially exclude their donation from transfusion. The volunteering of truthful and accurate information by a donor during health assessment is essential for the exclusion of donors whose blood may transmit diseases to recipients.

## Testing of Donor Blood

Testing of a sample of donor blood is required before units of blood or blood components are available for routine transfusion. The label on the container indicates the donor's ABO group and, when appropriate, Rh type. When "Rh Negative" is indicated, the blood has been tested and found negative for the presence of the D antigen including the weak expression of D (weak D).

A sample from each donation intended for allogeneic use has been tested by FDA-licensed tests and found negative for antibodies to human immunodeficiency virus (anti-HIV-1/2), hepatitis C virus (anti-HCV), human T-cell lymphotropic virus (anti-HTLV-I/II) and hepatitis B core antigen (anti-HBc), as well as HIV antigen (HIV-1-Ag) and hepatitis B surface antigen (HBsAg). A serologic test for syphilis has been performed and found to be negative. Alanine aminotransferase (ALT) testing is no longer required to qualify blood for transfusion.

For units intended for autologous use, the donor-patient will ordinarily have had a serologic test for syphilis and will have been tested for anti-HIV-1/2, HBsAg, anti-HCV, anti-HBc, and HIV-1-Ag. Units may have been tested for anti-HTLV-I/II and ALT. Autologous units remain acceptable for infusion to the donor-patient even if one or more of these tests are positive. A biohazard label will be applied to autologous units that are reactive for syphilis, repeatedly reactive for anti-HIV-1/2, HBsAg, anti-HCV, anti-HBc, and HIV-1-Ag, with confirmatory/supplemental test results either positive or not available. Autologous units drawn, stored, and infused at the same facility may not have been tested for disease markers.

Tests for unexpected antibodies against red cell antigens have been performed on samples from all donors. The results of these tests are negative or have been determined to be clinically insignificant unless otherwise indicated on the label. Other tests may have been performed on donor blood as indicated by information that has been provided by the blood bank or transfusion service on an additional label or tie tag, or in a supplement to this *Circular*.

## Blood and Component Labeling

All blood components identified in this *Circular* have the ISBT 128 product name listed in parenthesis after the currently recognized component name. ISBT 128 is a new system of identifying, naming, and barcoding blood components. Labels will contain the following information:

1. The proper name, whole blood or component, including an indication of any qualification or modification.
2. The method by which the component was prepared, either by whole blood or apheresis collection.
3. The temperature range in which the component is to be stored.
4. The preservatives and anticoagulant used in the preparation of the blood or components, when appropriate.
5. The standard contents or volume is assumed unless otherwise indicated on the label or in *Circular* supplements.
6. The number of units in pooled components and any sedimenting agent used during cytappheresis.

7. The name, address, registration number, and US license number (if applicable) of the collection and processing location.
8. The expiration date (and time if applicable), which varies with the method of preparation (open or closed system) and the preservatives and anticoagulant used. When the expiration time is not indicated, the product expires at midnight.
9. The donation (unit or pool) identification number.
10. The donor category (paid or volunteer, and autologous if applicable).
11. ABO group and Rh type.
12. Special handling information, as required.
13. Statements regarding recipient identification, this *Circular*, infectious diseases risk, and prescription requirement.

### **Instructions for Whole Blood and All Components**

The following general instructions pertain to Whole Blood and all the components described in this *Circular*:

1. All blood and blood components must be maintained in a controlled environment and stored under appropriate conditions as described in the *AABB Standards for Blood Banks and Transfusion Services*.
2. The intended recipient and the blood container must be properly identified before the transfusion is started.
3. Sterility must be maintained.
4. All blood components must be transfused through a filter. A standard (generally 170-260 micron) filter may be used. For bedside leukocyte reduction, a leukocyte reduction filter may be substituted for blood components that have not been previously leukocyte-reduced.
5. Cellular blood components should be mixed thoroughly before use.
6. No medications or solutions may be routinely added to or infused through the same tubing with blood or components except 0.9% Sodium Chloride, Injection (USP). Other solutions intended for intravenous use may be used in an administration set or added to blood or components under either of the following conditions: a) They have been approved for this use by the FDA or b) There is documentation available to show that addition to the component involved is safe and efficacious. ABO-compatible plasma, 5% Albumin, or Plasma Protein Fraction, or other suitable plasma expanders may be used with approval of the patient's physician.
7. Lactated Ringer's, Injection (USP) or other electrolyte solutions containing calcium should never be added to or administered concurrently with blood or components collected in an anticoagulant containing citrate.
8. Blood and components must be inspected immediately prior to issue. If upon visual inspection the container is not intact or the appearance is abnormal (presence of excessive hemolysis, a significant color change in the blood bag as compared with the tubing segments, floccular material, cloudy appearance or other problems, etc), it must not be used for transfusion.

9. Blood components have been prepared by techniques that aid in preserving sterility up to the time of expiration. If the container is entered in a fashion that violates the integrity of the system for any reason, the component expires 4 hours after entry if maintained at room temperature (20-24 C), or 24 hours after entry if refrigerated (1-6 C).
10. Blood components may be warmed if clinically indicated for situations such as exchange or massive transfusions, or for patients with cold-reactive antibodies. Warming must be accomplished using an FDA-cleared warming device so as not to cause hemolysis.
11. Some life-threatening reactions occur after the infusion of only a small volume of blood. Therefore, unless otherwise indicated by the patient's clinical condition, the rate of infusion should initially be slow. Periodic observation and recording of vital signs should occur during and after the transfusion to identify suspected adverse reactions.

If a transfusion reaction occurs, the transfusion must be discontinued immediately and appropriate therapy initiated. The infusion should not be restarted unless approved by transfusion service protocol. Specific instructions concerning possible adverse reactions shall be provided to the patient or a responsible caregiver when direct medical observation or monitoring of the patient will not be available after transfusion.

12. Transfusion should be completed within 4 hours and prior to component expiration. If it is anticipated that blood or components cannot be infused in 4 hours, they should be divided and stored appropriately in the blood bank until needed.
13. All adverse events related to transfusion, including possible bacterial contamination of a blood component or suspected disease transmission, must be reported to the transfusion service according to their local protocol.
14. Blood banks and transfusion services are referred to the AABB *Standards for Blood Banks and Transfusion Services* for additional information and policies, especially in the areas of recipient sample identification, compatibility testing, issue and transfusion of blood and blood components, investigation of transfusion reactions, and proper record-keeping practices.
15. Transfusionists are referred to the AABB *Technical Manual* for applicable chapters on adult and pediatric transfusion.
16. Transfusionists are directed to the specific product manufacturer's package insert for instructions pertaining to use of transfusion devices, eg, filters, blood administration sets, blood warmers.

### **Side Effects and Hazards**

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  $\geq 1$  C or 2 F occurring during or shortly after a transfusion and in the absence of any other pyrexia 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; 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 benefit from receiving leukocyte-reduced components; if these reactions are thought to be 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.

*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 received prior transfusions and may develop symptoms after infusion of very small amounts of IgA-containing plasma, in any transfusion component.

*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. The occurrence of TRALI is associated, in many cases, 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, however, 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 other blood components can only be detected by specialized testing.

3. *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 (ie, 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. Leukocyte-reduced components contain sufficient residual T lymphocytes that GVHD remains a risk. Gamma 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, eg, 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-1/2, HTLV-I/II, and hepatitis, as well as other agents. All blood and components released for transfusion have been found negative on approved tests for markers of infection with hepatitis B and C, HIV-1 and -2 (including HIV-1 antigen), and HTLV-I/II (see section on Testing of Donor Blood). These procedures do not totally eliminate the risk of transmitting these viruses.

*Cytomegalovirus* (CMV) may, unpredictably, be present in white-cell-containing components from donors previously infected with this virus, which can persist life-long 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* sp., *Bartonella* sp., *Borrelia* sp., *Brucella* sp., the agent of Colorado tick fever, *Leishmania* sp., *Parvovirus* sp., plasmodia, rickettsia, *Toxoplasma* sp., and certain trypanosomes.

2. *Bacterial contamination* occurs rarely but can cause acute, severe, sometimes life-threatening effects. Onset of high fever ( $\geq 2$  C or  $\geq 3.5$  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. At rapid infusion use of a blood warming device should be considered. 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. Body stores of calcium are large and citrate is, ordinarily, promptly metabolized by the liver, so 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.

## **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](mailto:fatalities2@cber.fda.gov)). Within 7 days after the fatality, a written report must be submitted to the Director, Office of Compliance and Biologics Quality, HFM-600, CBER, FDA, 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](http://www.fda.gov/cber/transfusion.htm).

## **Components Containing Red Blood Cells**

### **Whole Blood and other Red-Cell-Containing Components**

#### *Description*

Red cells contain hemoglobin and serve to transport oxygen through the bloodstream and to the tissues. Whole Blood contains the red cells and plasma constituents of circulating blood; the primary red-cell-containing transfusion component is Red Blood Cells, prepared by centrifugation or sedimentation of Whole Blood to remove many of the platelets and white cells of circulating blood and much of the plasma. Red cell components can be prepared by Whole Blood collection or by apheresis.

Depending upon the collection system used, a single whole blood donation typically contains either 450 mL ( $\pm 10\%$ ) or 500 mL ( $\pm 10\%$ ) of blood with a minimum hematocrit of 38%, withdrawn in a sterile container that contains an anticoagulant solution licensed for this use. Occasionally Whole Blood units of other volumes are collected.

Whole Blood can be stored for an interval ("shelf life") determined by the properties of the anticoagulant-preservative solution. Anticoagulant Citrate Dextrose Solutions ACD-A and ACD-B are older anticoagulants that are seldom used for whole blood collection. Anticoagulant Citrate Phosphate Dextrose Solution (CPD) and Citrate Phosphate Double Dextrose Solution (CP2D) contain trisodium citrate at a concentration of 26.3 g/L, citric acid at 3.27 g/L, and monobasic sodium phosphate at 2.22 g/L; CPD has 25.5 g/L of dextrose and CP2D has 51.1 g/L of dextrose. Anticoagulant Citrate Phosphate Dextrose Adenine Solution (CPDA-1) has the same concentrations of citric acid, trisodium citrate, and monobasic phosphate as the other formulas, with 31.9 g/L of dextrose and 0.275 g/L of adenine. CPD, CP2D, and CPDA-1 are prepared sterilely in the empty Whole Blood container at a ratio of 14 mL per 100 mL ( $\pm 10\%$ ) whole blood collected.

After plasma is removed, the resulting component is Red Blood Cells, a component that has a hematocrit of 65-80% and a usual volume between 225 and 350 mL. Additive solutions (AS) may be mixed with the red cells remaining after removal of nearly all of the plasma. The typical hematocrit of AS Red Blood Cells is 55-65% and their volume is approximately 300-400 mL.

Red Blood Cells can also be collected by apheresis. This component must be collected in approved anticoagulants. The red cell volume collected and the anticoagulant used are noted on the label.

Descriptions of specific red-cell-containing components are given at the end of this section.

### ***Actions***

Whole Blood and all Red Blood Cell components increase the recipient's oxygen-carrying capacity by increasing the mass of circulating red cells. Processing and/or storage deplete the component of virtually all potential therapeutic benefit attributable to the functions of white cells and platelets; cellular elements do remain in the preparation and may cause adverse immunologic or physiologic consequences. Residual plasma in the component provides the recipient with volume expansion and nonlabile plasma proteins to the extent that residual plasma is present in the preparation. Depending on the method of production, Red Blood Cells may contain from approximately 20 mL to 150 mL of residual plasma.

### ***Indications***

Red-cell-containing components are indicated for treatment of symptomatic deficit of oxygen-carrying capacity. They may be indicated for exchange transfusion. Acute hypovolemia of sufficient degree to be associated with shock may be treated with Whole Blood or with Red Blood Cell components combined with volume expanders.

### ***Contraindications***

Except when the patient's symptoms require immediate enhancement of oxygen-carrying capacity, red-cell-containing components should not be used to treat anemias that can be corrected with specific medications such as iron, vitamin B<sub>12</sub>, folic acid, or recombinant erythropoietin.

Whole Blood and Red Blood Cells should not be used as volume expanders or to increase oncotic pressure of circulating blood.

Coagulation deficiencies should be treated with components or blood derivatives appropriate for the deficiencies present.

### ***Dosage and Administration***

Each unit of Whole Blood or Red Blood Cells contains enough hemoglobin to raise the hemoglobin concentration in an average-sized adult by approximately 1 g/dL (raise hematocrit by 3 percentage points). Smaller aliquots may be available for use with neonatal or pediatric patients, or adults with special transfusion needs.

The ABO group of all red-cell-containing components must be compatible with ABO antibodies in the recipient's plasma. Whole Blood must be ABO-identical with the recipient; Red Blood Cells, which contain a much-reduced volume of antibody-containing plasma, need not be ABO-identical.

Except in cases when any delay in transfusion will be life-threatening, serologic compatibility between recipient and donor must be established before any red-cell-containing component is transfused. This may be accomplished by type and screen, crossmatching, or by use of electronic selection (“computer crossmatch”).

The initial portion of each transfusion should be infused slowly and with sufficient observation to detect onset of acute immunologic or infectious complications. Thereafter, the rate of infusion can be more rapid, as tolerated by the patient’s circulatory system. It is undesirable for red-cell-containing components to remain at room temperature longer than 4 hours. If the anticipated infusion rate must be so slow that the entire unit cannot be infused within 4 hours, it may be appropriate to order smaller aliquots for transfusion.

### *Side Effects and Hazards*

Hazards that pertain to all transfusion components are described in the earlier section entitled Side Effects and Hazards. Listed below are hazards that apply 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. 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; or e) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies. 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 post-reaction 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.

*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.

### Components Available

1. **Red Blood Cells (RED BLOOD CELLS)** are prepared from blood collected into any of the anticoagulant-preservative solutions approved by the FDA, and separated from the plasma by centrifugation or sedimentation. Separation may be done at any time during the allowable storage interval ("shelf life"). Red Blood Cells may contain from 160-275 mL of red cells (50-90 g of hemoglobin) suspended in varying quantities of residual plasma. Units of Whole Blood that are less than 405 mL (450 mL  $\pm$  10%) are sometimes collected and prepared into **Red Blood Cells, Low Volume (RED BLOOD CELLS LOW VOLUME)**. These preparations may require adjustment of the anticoagulant solution supplied in standard blood collection containers.
2. **Red Blood Cells, Adenine Saline Added (RED BLOOD CELLS ADENINE SALINE ADDED)** are prepared by centrifuging whole blood to remove as much plasma as possible, and replacing the plasma with usually 100-110 mL of an additive solution that contains some combination of dextrose, adenine, sodium chloride, and either monobasic sodium phosphate (AS-3) or mannitol (AS-1 and AS-5); the hematocrit is usually between 55 and 65%. Red cells in an additive solution have lower viscosity than Red Blood Cells, and flow through administration systems in a manner more comparable to that of Whole Blood. Red cells stored with an additive solution have an extended shelf life.

3. **Red Blood Cells Leukocytes Reduced (RED BLOOD CELLS LEUKOCYTES REDUCED)** are described in the later section on Further Processing.
4. **Red Blood Cells Frozen (FROZEN RED BLOOD CELLS)** and **Red Blood Cells Rejuvenated Frozen (FROZEN REJUVENATED RED BLOOD CELLS)** are prepared by adding glycerol to red cells as a cryoprotective agent before freezing. The glycerol must be removed from the thawed component before it is infused. Frozen red cells may be stored for up to 10 years, and for longer intervals if there is particular need for specific units. Frozen storage is especially suitable for red cells with unusual antigenic phenotypes and for autologous donations when liquid-preserved blood cannot fulfill demands.
5. **Red Blood Cells Deglycerolized (DEGLYCEROLIZED RED BLOOD CELLS)** is the form in which cryopreserved red cells (Red Blood Cells Frozen) are available for infusion. Glycerol is added to red cells as a cryoprotective agent before freezing, and must be removed from the thawed component before it is infused.

Red Blood Cells Deglycerolized contain 80% or more of the red cells present in the original unit of blood, and have approximately the same expected post-transfusion survival as Red Blood Cells. Glycerol is removed by washing the cells with successively lower concentrations of Sodium Chloride Injection (USP); the final suspension is in 0.9% Sodium Chloride, Injection (USP), with or without small amounts of dextrose. Small amounts of residual free hemoglobin may cause the supernatant fluid to be pink-tinged.

Red Blood Cells Deglycerolized provide the same physiologic benefits as Red Blood Cells, but their use is usually restricted to situations in which standard transfusion components are inappropriate or unavailable. Red Blood Cells Deglycerolized may be useful for red cell transfusions to patients with clinically significant immune reactivity against IgA or other plasma constituents, because the extensive washing required to remove glycerol also efficiently removes plasma constituents.

In addition to the side effects and hazards of red cell transfusion, Red Blood Cells Deglycerolized carry a risk of intravascular hemolysis if deglycerolization has been inadequate.
6. **Red Blood Cells Rejuvenated (REJUVENATED RED BLOOD CELLS)** may be prepared from red cells stored in appropriate anticoagulants up to 3 days after expiration. Addition of an FDA-approved solution containing inosine, phosphate, and adenine restores 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) to levels approximating those of freshly drawn cells. Red Blood Cells Rejuvenated must be washed before infusion to remove the inosine, which may be toxic. Red Blood Cells Rejuvenated may be prepared for frozen storage by standard glycerolization, which also serves to remove inosine.
7. **Red Blood Cells Rejuvenated Deglycerolized (DEGLYCEROLIZED REJUVENATED RED BLOOD CELLS)** is the form in which rejuvenated, cryopreserved red cells (Red Blood Cells Frozen Rejuvenated) are available for infusion. For additional information, see sections on Red Blood Cells Rejuvenated and Red Blood Cells Deglycerolized above.
8. **Whole Blood (WHOLE BLOOD)** is rarely used for transfusion because sound resource management usually demands preparation of several components from a single blood donation.

9. **Red Blood Cells Pheresis (APHERESIS RED BLOOD CELLS)** are red cells collected by apheresis. The dosage can be calculated, as for Red Blood Cells, from the red cell content of the product. Red Blood Cells Pheresis contains on average 60 g of hemoglobin per unit. For comparison, a typical unit of Red Blood Cells derived from a whole blood collection contains 50 to 80 g of hemoglobin.
10. Any of the above may be **irradiated**. See section on Further Processing.

## **Plasma Components**

### **Fresh Frozen Plasma and Plasma Components Containing Functional Factors V and VIII (Labile Coagulation Factors)**

#### ***Description***

Fresh Frozen Plasma (FFP) consists of the fluid portion of blood that is separated and placed at  $-18^{\circ}\text{C}$  or below within 8 hours after collection of whole blood if the anticoagulant solution is CPD, CP2D, or CPDA-1. Plasma collected in ACD or 2-3% Sodium Citrate must be placed at  $-18^{\circ}\text{C}$  or below within 6 hours. Plasma components may be prepared from whole blood collection or by apheresis. The anticoagulant solution used is indicated on the label. Component volume varies depending on the method used to collect and prepare the component. Component volume is indicated on the label. By definition each mL of undiluted plasma contains 1 international unit (IU) of each coagulation factor.

#### ***Action***

FFP serves as a source for deficient or defective plasma proteins.

#### ***Indications***

FFP is indicated in the following conditions:

1. Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors.
2. Patients with massive transfusion who have clinically significant coagulation abnormalities.
3. Patients on coumadin who are bleeding or need to undergo an invasive procedure before Vitamin K could reverse the coumadin effect.
4. Patients with thrombotic thrombocytopenic purpura (TTP).
5. Management of patients with selected coagulation factor deficiencies for which no concentrates are available.
6. Management of patients with rare specific plasma protein deficiencies, such as C-1-esterase.

### ***Contraindications***

Do not use FFP when coagulopathy can be corrected more effectively with specific therapy, such as vitamin K, Cryoprecipitated AHF, or Factor VIII:C concentrates.

Do not use FFP when blood volume can be safely and adequately replaced with other volume expanders.

### ***Dosage and Administration***

Compatibility tests before transfusion are not necessary. Plasma must be ABO-compatible with the recipient's red cells. The volume transfused depends on the clinical situation and patient size, and may be guided by laboratory assays of coagulation function.

Do not use the frozen component if there is evidence of container breakage or of thawing during storage. Plasma must be thawed in a waterbath at 30-37 C or in an FDA-cleared device. If a waterbath is used, thaw FFP in a protective plastic overwrap using gentle agitation. Thawed FFP must be infused immediately or stored at 1-6 C for up to 24 hours. If not used within 24 hours, the words "fresh frozen" must be removed.

### ***Side Effects and Hazards***

Hazards that pertain to all transfusion components are described in the earlier section on Side Effects and Hazards.

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

### **Components Available**

1. **Fresh Frozen Plasma (FRESH FROZEN PLASMA)** contains plasma proteins including all coagulation factors.
2. **Fresh Frozen Plasma Donor Retested (FRESH FROZEN PLASMA QUARANTINED RETESTED)** is identical in all aspects to FFP except that it is held in quarantine for a minimum of 112 days from collection, until the donor from whom it is prepared has been retested and found negative for all FDA-required and recommended tests. By using this testing, which is intended to reduce the risk of virus transmission, blood centers accept plasma only from donors who have been retested beyond the probable infectious window periods. The potential hazards of FFP Donor Retested are identical to FFP except that the risk of pathogen transmission due to units collected from donors in the seronegative window period for those tests performed will be reduced.

### **Plasma Components Containing Reduced Amounts of Labile Coagulation Factors**

#### ***Description***

Other Plasma components may be made from whole blood collected in all approved anti-coagulants or by apheresis. These components contain stable coagulation factors such as

Factor IX and fibrinogen in concentrations similar to that of FFP, but reduced amounts of Factors V and VIII. The volume is indicated on the label.

### ***Actions***

These components serve as a source of defective or deficient plasma proteins except for Factor V and Factor VIII.

### ***Indications***

As for FFP, except that these components should not be used to treat coagulation factor deficiencies of Factor V and Factor VIII:C.

### ***Contraindications***

Do not use Plasma, Thawed Plasma, or Liquid Plasma for replacement of coagulation Factors V and VIII. Otherwise, the contraindications are the same as for FFP.

### ***Dosage and Administration***

Same as for FFP.

### ***Side Effects and Hazards***

Same as for FFP.

### **Components Available**

1. **Thawed Plasma (THAWED PLASMA)** is derived from FFP prepared in a closed system, thawed at 30-37 C, and maintained at 1-6 C for 1-5 days.
2. **Plasma Frozen Within 24 Hours After Phlebotomy (PLASMA FROZEN WITHIN 24 HOURS OF PHLEBOTOMY)** must be separated and placed at -18 C or below within 24 hours from whole blood collection.
3. **Plasma; Liquid Plasma (PLASMA, LIQUID PLASMA)** is separated no later than 5 days after the expiration date of the Whole Blood. Plasma may be stored at -18 C or below. Liquid Plasma is stored at refrigerator temperature (1-6 C).

### **Plasma, Cryoprecipitate Reduced (PLASMA CRYOPRECIPITATE REDUCED)**

#### ***Description***

Plasma, Cryoprecipitate Reduced (PLASMA CRYOPRECIPITATE REDUCED) is prepared from FFP or FFP Donor Retested by a process of rapid freezing, followed by thawing and centrifugation, which removes the cryoprecipitate and yields plasma that is deficient in Factor VIII, von Willebrand factor (vWF), fibrinogen, cryoglobulin, and fibronectin. Proteins such as albumin, Factors II, V, VII, IX, X, and XI remain in the

same concentration as in FFP. The high-molecular-weight forms of vWF (multimers) are more thoroughly removed by the process than smaller multimers.

### ***Action***

This component serves as a source for deficient or defective plasma proteins except for fibrinogen, Factor VIII, Factor XIII, and vWF.

### ***Indications***

Plasma, Cryoprecipitate Reduced is used in patients with thrombotic thrombocytopenic purpura (TTP) refractory to FFP. It may be used for the provision of clotting factors except Factor I (fibrinogen), Factor VIII, and vWF.

### ***Contraindications***

This component should not be used as a substitute for FFP in patients with congenital deficiencies of fibrinogen, Factor VIII, or vWF.

### ***Dosage and Administration***

Same as for FFP.

### ***Side Effects and Hazards***

Same as for FFP.

## **Cryoprecipitate Components**

### **Cryoprecipitated AHF; Cryoprecipitated AHF, Pooled (CRYOPRECIPITATED AHF, POOLED CRYOPRECIPITATED AHF, APHERESIS CRYOPRECIPITATED AHF)**

#### ***Description***

Cryoprecipitated AHF is prepared by thawing FFP between 1-6 C and recovering the precipitate. The cold-insoluble precipitate is refrozen within 1 hour. Cryoprecipitated AHF contains coagulation Factor VIII:C, Factor XIII, fibrinogen, vWF (Factor VIII:vWF), and fibronectin. Each unit of Cryoprecipitated AHF should contain  $\geq 80$  IU Factor VIII:C units and  $\geq 150$  mg of fibrinogen in approximately 15 mL of plasma.

If the label indicates "Cryoprecipitated AHF, Pooled," several units of Cryoprecipitated AHF have been pooled. The volume of the pool is indicated on the label and, if used, the volume of 0.9% Sodium Chloride, Injection (USP) added may be separately listed. To determine the minimum potency of this component, assume 80 IU of Factor VIII:C and 150 mg of fibrinogen for each unit of Cryoprecipitated AHF indicated on the label.

This component may be prepared from Whole Blood or Apheresis Fresh Frozen Plasma collected in any approved anticoagulant solution.

### ***Action***

Provides Factor VIII, fibrinogen, vWF, and Factor XIII

### ***Indications***

This component is indicated as second-line therapy for von Willebrand's disease and hemophilia A (Factor VIII:C deficiency). Concentrates are the preferred components when blood component therapy is needed for management of von Willebrand's disease and Factor VIII:C deficiency. **Cryoprecipitate should be used only if virus-inactivated Factor VIII concentrates are not available for management of patients with hemophilia A or von Willebrand's disease.** It is also used in the control of bleeding associated with fibrinogen deficiency and to treat Factor XIII deficiency. Indications for use as a source of fibronectin are not clear.

### ***Contraindications***

Do not use this component unless results of laboratory studies indicate a specific hemostatic defect for which this product is indicated.

### ***Dosage and Administration***

Compatibility testing is unnecessary. ABO-compatible material is preferred. Rh type need not be considered when using this component.

The frozen component is thawed in a protective plastic overwrap in a waterbath at 30-37 C up to 15 minutes (thawing time may need to be extended if product is pooled before freezing). Product should not be given if there is evidence of container breakage or of thawing during storage. Product is not to be refrozen after thawing. Thawed Cryoprecipitated AHF 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; or within 4 hours if it is an open system or units have been pooled after thawing.

For pooling, the precipitate in each concentrate should be mixed well with 10-15 mL of diluent to ensure complete removal of all material from the container. The preferred diluent is 0.9% Sodium Chloride, Injection (USP). Cryoprecipitated AHF, pooled prior to freezing requires no extra diluent.

For treatment of bleeding in patients with hemophilia A, rapid infusion of a loading dose expected to produce the desired level of Factor VIII:C is usually followed by a smaller maintenance dose every 8-12 hours. To maintain hemostasis after surgery, a regimen of therapy for 10 days or longer may be required. If circulating antibodies to Factor VIII:C are present, the use of larger doses, activated concentrates, porcine-derived concentrates, or other special measures may be indicated.

In the steady state, the half-life of fibrinogen is 3-5 days. Dosing schedules of

cryoprecipitate infusions every 3 days may be appropriate for patients with congenital hypofibrinogenemia. Thrombosis alters fibrinogen kinetics; therefore, patients receiving cryoprecipitate as fibrinogen replacement in conditions associated with increased fibrinogen turn-over should be monitored with fibrinogen assays.

To calculate cryoprecipitate dosage as a source of Factor VIII, the following formula is helpful:

$$\text{Number of bags of cryoprecipitate required} = \frac{\text{desired increased Factor VIII:C level (in \%)} \times \text{patient's plasma volume (in mL)*}}{\text{average units of Factor VIII:C per cryoprecipitate (minimum 80)}}$$

For example:

$$\frac{50\% \times 2800 \text{ mL}}{80} \quad \text{or} \quad \frac{0.50\text{U/ML} \times 2800 \text{ mL}}{80 \text{ U/bag}} = 18 \text{ bags}$$

\*or substitute 4% body weight (kg)  $\times$  1000

Good patient management requires that the Cryoprecipitated AHF treatment responses of Factor VIII-deficient recipients be monitored with periodic plasma Factor VIII:C assays.

For treatment of von Willebrand's disease, smaller amounts of Cryoprecipitated AHF will correct the bleeding time. These patients should be monitored by appropriate laboratory studies to determine frequency of Cryoprecipitated AHF administration.

### ***Side Effects and Hazards***

Hazards that pertain to all transfusion components are described in the earlier section on Side Effects and Hazards.

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

## **Platelet Components**

### **Platelets (PLATELETS)**

#### ***Description***

A unit of Platelets is a concentrate of platelets separated from a single unit of Whole Blood and suspended in a small amount of the original plasma. One unit of Platelets should contain no fewer than  $5.5 \times 10^{10}$  platelets suspended in 40-70 mL of plasma, which contains normal levels of stable coagulation factors. Depending upon the technique

used in preparation, each platelet unit may contain a large number of leukocytes. Some platelet units may contain more than the trace amounts of red cells usually present, which imparts a pink-to-salmon colored appearance. This component may be prepared from Whole Blood collected in all approved anticoagulant solutions.

### ***Actions***

Platelets are essential for normal hemostasis. Complex reactions between platelet receptors, phospholipid, and thrombin induce platelet activation, which leads to platelet aggregation and formation of a primary hemostatic plug. The therapeutic goal of platelet transfusion is to provide adequate numbers of normally functioning platelets for the prevention or cessation of bleeding.

### ***Indications***

Platelet transfusion is indicated for treatment of patients bleeding due to critically decreased circulating platelet count or functionally abnormal platelets. Platelet transfusions are not usually effective or indicated in patients with destruction of circulating platelets due to autoimmune disorders, eg, immune thrombocytopenic purpura (ITP).

Platelets may be useful if given prophylactically to patients with rapidly decreasing or low platelet counts (usually less than 10,000/ $\mu$ L) secondary to cancer or chemotherapy. Platelet transfusion may also be useful in selected cases of postoperative bleeding, eg, platelet count less than 50,000/ $\mu$ L. If platelet function is normal, platelets should not be transfused if the platelet count is greater than 100,000/ $\mu$ L.

### ***Contraindications***

Do not use this component if bleeding is unrelated to decreased numbers of or abnormally functioning platelets.

Do not use in patients with destruction of endogenous and exogenous platelets, such as in TTP or ITP, unless the patient has a life-threatening hemorrhage.

### ***Dosage and Administration***

Compatibility testing is not necessary in routine platelet transfusion. The donor plasma in platelets should be ABO-compatible with the recipient's red cells, especially when this component is to be transfused to infants. The number of platelet units to be administered depends on the clinical situation of each patient. One unit of Platelets would be expected to increase the platelet count of a 70-kg adult by 5-10,000/ $\mu$ L and increase the count of an 18-kg child by 20,000/ $\mu$ L. The usual dose in an adult patient is 4-8 units. This dose may need to be repeated in 1-3 days because of the short lifespan of transfused platelets (3-4 days). The corrected count increment (CCI) is a more precise method for measuring platelet response. This method determines the increase in platelet count adjusted for the number of platelets infused and the size of the recipient. The formula for CCI is as follows:

$$\text{CCI} = \frac{\text{Posttransfusion platelet count/mL} - \text{pretransfusion platelet count/mL}}{\text{Number of platelets transfused} \times 10^{11}} \times \text{body surface area (m}^2\text{)}$$

For example:

A patient with acute myelogenous leukemia with a nomogram-derived body surface area of 1.40 m<sup>2</sup> is transfused with a unit of Platelets Pheresis. The collecting facility label indicates a platelet dose of 4.5 × 10<sup>11</sup>. The pretransfusion platelet count was 2000/μL. The patient's platelet count from a sample of blood collected 15 minutes after platelet transfusion was 29,000/μL.

$$\text{CCI} = \frac{29,000 - 2000}{4.5 \times (10^{11})} \times 1.4 = 8400$$

A CCI of at least 5000 is expected. Poorer responses are sometimes seen. See Platelet Alloimmunization.

Platelets must be examined prior to administration. Units with excessive aggregates should not be administered. Transfusion may proceed as fast as tolerated but must take less than 4 hours.

### *Side Effects and Hazards*

Hazards that pertain to all transfusion components are described in the section on Side Effects and Hazards. 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. Gram's stain of suspected contaminated units of Platelets, Platelets Pheresis, or Platelets Pooled may be helpful. Prompt management including broad-spectrum antibiotic therapy along with culture of patient sample, implicated unit, and administration set is important.
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 distinguish immune from nonimmune platelet refractoriness by assessing platelet recovery soon after infusion, ie, 10-60 minute postinfusion platelet increment. In immune refractory states secondary to serologic incompatibility, there is poor recovery in the early postinfusion interval. In nonimmune mechanisms (ie, splenomegaly, sepsis, fever, intravascular devices, and DIC) platelet recovery within 1 hour of infusion may be adequate while longer-term survival (ie, 24-hour survival)

is reduced. Serologic tests may 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 are given to an Rh-negative female of childbearing potential, prevention of D immunization by use of Rh Immune Globulin should be considered. In some patients, Platelets suspended in 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.

### Components Available

1. **Platelets (PLATELETS)**

A unit of Platelets is a concentrate of platelets separated from a single unit of Whole Blood and suspended in a small amount of the original plasma.

2. **Platelets Pooled (POOLED PLATELETS)**

Platelets Pooled is composed of individual platelet units combined by sterile technique and has an allowable shelf life of 4 hours. The number of units of Platelets in the pool will be indicated on the label. To determine the minimum potency of this component, assume  $5.5 \times 10^{10}$  platelets per unit of Platelets indicated on the label. See the label for the approximate volume.

3. **Platelets Pheresis (APHERESIS PLATELETS)**

Apheresis is an effective way to harvest a therapeutic adult dose of platelets from a single donor. Platelets Pheresis should contain  $\geq 3 \times 10^{11}$  platelets. One unit of Platelets Pheresis may replace 4-8 units of Platelets. The exact number of platelets in the apheresis product can be obtained on request from the collecting facility. The volume of plasma used for platelet suspension varies between 100 and 500 mL. (See the label for the approximate volume.) The number of leukocytes contained in this component varies depending upon the blood cell separator and protocol used for collection. Platelets Pheresis is supplied in a large plastic pack or in two connected packs to improve platelet viability during storage by providing more surface area for gas exchange. Anticoagulant solutions currently used for the collection and preservation of Platelets Pheresis include ACD-A and ACD-B.

In patients refractory to platelets from unmatched donors, this component may be especially useful if HLA-matched or if determined recipient-compatible by serologic methods. Other causes of refractoriness to Platelets include disseminated intravascular coagulation (DIC), ITP, hypersplenism, fever, and sepsis; for these latter conditions, Platelets Pheresis is no more effective than Platelets.

Red blood cell compatibility testing is necessary only if the component is prepared by a method that allows the component to contain 2 mL or more of red cells.

4. **Platelets Pheresis Leukocytes Reduced (APHERESIS PLATELETS, LEUKOCYTES REDUCED)**

Platelets collected by apheresis may contain a therapeutic adult dose of platelets and very few leukocytes. If the leukocyte content is  $\leq 5 \times 10^6$  and the platelet count is  $\geq 3 \times 10^{11}$  platelets, the unit can be labeled Platelets Pheresis Leukocytes Reduced. The volume, anticoagulant/preservative and storage conditions are the same as those for

Platelets Pheresis. If Platelets Pheresis is further processed using leukocyte reduction filters as a separate manufacturing step, the unit may be labeled Platelets Pheresis Leukocytes Reduced provided that the residual leukocyte count is  $\leq 5 \times 10^6$  and the platelet recovery is at least 85% of the prefiltration product. Platelets Pheresis Leukocytes Reduced is indicated for the prevention of recurrent febrile, nonhemolytic transfusion reaction, HLA alloimmunization and transfusion-transmitted CMV infection. (See section on Further Processing.)

## Granulocyte Components

### Granulocytes Pheresis and Granulocytes/Platelets Pheresis (GRANULOCYTES APHERESIS GRANULOCYTES, APHERESIS GRANULOCYTES/ PLATELETS)

#### *Description*

Granulocyte concentrates are collected by a hemapheresis technique. Granulocytes Pheresis usually contains many other leukocytes and platelets as well as 20-50 mL of red cells. The number of granulocytes in each concentrate is  $\geq 1.0 \times 10^{10}$ . Various modalities may be used to improve granulocyte harvest, including administration of growth factor or hormones. The Granulocytes Pheresis component is usually suspended in 200-300 mL of anticoagulant and plasma as indicated on the label.

Red cell sedimenting agents approved by the FDA, such as hydroxyethyl starch (HES), may be used in the collection of granulocytes. If used, residual agent will be present in the final component. (See label.) Granulocytes Pheresis should be administered as soon after collection as possible due to well-documented deterioration of granulocyte function on short-term storage. If stored, maintain at 20-24 C without agitation for no more than 24 hours.

The component Granulocytes/Platelets Pheresis is similar to both Granulocytes Pheresis and Platelets Pheresis in actions, side effects, hazards, and the need for irradiation. It is indicated for patients with simultaneous need for both of these components. The expected potency of the component is usually greater than  $3 \times 10^{11}$  platelets and  $1 \times 10^{10}$  granulocytes. Administration is the same as for Granulocytes Pheresis, because granulocyte therapy is the primary therapeutic consideration.

#### *Actions*

Granulocytes migrate toward, phagocytize, and kill bacteria and fungi. A quantitative relationship exists between the level of circulating granulocytes and the prevalence of bacterial and fungal infection in neutropenic patients.

The infusion of a granulocyte concentrate in itself is rarely associated with an increment in the patient's granulocyte count. This may be due to the sequestration of granulocytes that results from prior immunization to leukocyte antigens or due to consumption of granulocytes in the infection process.

### *Clinical Use*

Granulocytes Pheresis is used typically in treatment of neutropenic patients (generally less than  $0.5 \times 10^9/L$  [ $500/\mu L$ ]) who have documented infections, especially gram-negative bacteria and fungi, and who have not responded to antibiotics. A trial of broad-spectrum antimicrobial agents should be used before granulocyte transfusion therapy is initiated.

If eventual marrow recovery is not expected, granulocyte transfusion is not indicated. Prophylactic use of granulocytes in noninfected patients is not recommended. If the intended recipient is CMV-seronegative and severely immunosuppressed (eg, a marrow transplant recipient), CMV-seropositive granulocytes should not be given.

### *Dosage and Administration*

Transfuse as soon as possible through a standard blood filter. The red cells in Granulocytes Pheresis must be ABO-compatible with the recipient's antibodies. Depth-type microaggregate filters and leukocyte reduction filters remove granulocytes and should not be used when transfusing this component. Once granulocyte transfusion therapy is initiated, support should continue at least daily until infection is cured, defervescence occurs, the absolute granulocyte count returns to at least  $0.5 \times 10^9/L$  ( $500/\mu L$ ), or the physician in charge decides to halt the therapy.

Since most patients receiving these products are severely immunosuppressed, Granulocytes Pheresis are generally irradiated to prevent graft-vs-host disease (see section on Further Processing).

### *Side Effects and Hazards*

Hazards that pertain to all transfusion components are described in the section on Hazards and Side Effects. Listed below are hazards that apply specifically to granulocyte concentrates.

1. **Febrile, Nonhemolytic Reactions:** These reactions are frequently noted in patients receiving granulocyte transfusions. The occurrence of chills, fever, and pulmonary insufficiency in patients receiving granulocyte components may be avoided or lessened by slow administration and the use of meperidine.
2. **Allergic Reactions:** Allergic reactions to HES and other red cell sedimenting solutions may occur during granulocyte transfusion.

## **Further Processing**

This section addresses further processing of previously described blood components (original components) after collection and initial laboratory testing. The indications addressed in this section refer to the reasons for requiring special components and not the original therapeutic indication associated with the request for the original component. One or more of these processes may be performed on a component.

**Leukocyte-Reduced Components****Red Blood Cells Leukocytes Reduced; (RED BLOOD CELLS LEUKOCYTES REDUCED)****Platelets Leukocytes Reduced; (PLATELETS LEUKOCYTES REDUCED)****Platelets Pheresis Leukocytes Reduced (APHERESIS PLATELETS LEUKOCYTES REDUCED)*****Description***

A unit of whole blood contains  $\geq 1-10 \times 10^9$  white cells. Leukocyte-reduced blood is prepared by filtering blood with special filters that remove white cells by sieving and adherence mechanisms. Filtration may be done as follows: 1) soon after collection (prestorage), 2) after varying periods of storage in the laboratory, or 3) at the bedside. The method used in the laboratory for leukocyte reduction is subject to quality control testing; leukocyte-reduced components prepared at the bedside are not. Leukocyte reduction will decrease the cellular content and volume of blood according to characteristics of the filter system used. Whole Blood, Red Blood Cells, and Platelets Pheresis Leukocytes Reduced must have a residual content of leukocytes  $< 5 \times 10^6$ . Platelets Leukocytes Reduced must have  $< 8.3 \times 10^5$  residual leukocytes. Leukocyte reduction filters variably remove other cellular elements in addition to white cells. Retention of 85% of the original therapeutic component is required.

***Actions***

The leukocyte-reduced red cell component will have therapeutic efficacy equal to at least 85% of the original component (see actions of appropriate blood component). For pre-storage leukocyte-reduced Platelets and Platelets Pheresis, the quality control standards are the same as for unfiltered products.

***Indications***

Leukocyte-reduced components are indicated for prevention of recurrent febrile, non-hemolytic transfusion reactions. These components have been shown to reduce the incidence of HLA alloimmunization. They have also been shown to reduce the risk of transfusion-transmissible CMV. These components may also be beneficial in reducing transfusion-related immunomodulation, but this use should be considered experimental.

***Contraindications***

Do not use leukocyte-reduced components to prevent GVHD. Do not use leukocyte-reduction filters to infuse Granulocytes.

***Dosage and Administration***

Components that are leukocyte-reduced in the laboratory must be transfused through a blood administration set containing a standard blood (generally 170-260 micron) filter. Administration instructions are those for the original component.

***Side Effects and Hazards***

Same as for original component. The use of blood components that are leukocyte-reduced at the bedside may cause unexpected severe hypotension in some recipients, particularly those on ACE inhibitor medication.

**CMV-Negative Blood*****Description***

CMV-seronegative blood is selected by performing testing for antibodies to CMV (using a CMV test approved for donor screening.) The component is otherwise similar to its original component. Since transmission of CMV disease is associated with cellular blood components, FFP, cryoprecipitate, and other plasma-derived blood components do not require special testing.

***Actions***

Same as for original component.

***Indications***

Transfusion of CMV-negative blood is indicated in recipients who are at risk for severe CMV infections. The groups at risk for such untoward effect include fetuses and low-birthweight infants, CMV-seronegative pregnant women, CMV-seronegative marrow transplant recipients, CMV-seronegative solid-organ transplant recipients, severely immunosuppressed CMV-seronegative recipients, and CMV-seronegative HIV-infected patients.

***Contraindications***

CMV-seropositive patients and recipients of CMV-seropositive organs do not require CMV-seronegative components. Otherwise, see Contraindications section of original component.

***Dosage and Administration***

The same as for original component.

***Side Effects and Hazards***

Same as for original component except for CMV disease.

**Irradiated Blood*****Description***

Blood components that contain viable lymphocytes may be irradiated to prevent proliferation of T lymphocytes, which is the immediate cause of GVHD. Irradiated blood is prepared by exposing the component to a source of gamma irradiation. To eliminate the proliferative capacity of leukocytes, the central midplane of the canister should receive 2500 cGy and the lowest dose delivered to any portion of the canister should be 1500 cGy. Any blood component can be irradiated. The therapeutic dose and benefits are not affected by this level of irradiation.

***Actions***

Same as for original component.

***Indications***

Irradiated blood is indicated for use in patient groups that are at risk for GVHD from transfusion. At-risk groups include: fetuses receiving intrauterine transfusions, selected immunoincompetent or immunocompromised recipients, recipients of cellular components known to be from a blood relative, recipients who have undergone marrow or peripheral blood progenitor cell transplantation, and recipients of cellular components whose donor is selected for HLA compatibility.

***Contraindications***

Same as for original component.

***Dosage and Administration***

The same as original component. It is acceptable to give irradiated cells to a recipient other than the originally intended recipient.

***Side Effects and Hazards***

Irradiation induces erythrocyte membrane damage. Irradiated red cells have been shown to have higher supernatant potassium levels than nonirradiated red cells. Removal of residual supernatant plasma prior to transfusion may reduce the risks associated with elevated plasma potassium. The expiration date of irradiated red cells is changed to 28 days postirradiation if available shelf life exceeds 28 days. Otherwise, the side effects are similar to those of the original component.

**Washed Components****Red Blood Cells Washed (WASHED RED BLOOD CELLS)****Platelets Washed (WASHED PLATELETS)****Platelets, Pheresis Washed (WASHED APHERESIS PLATELETS)*****Description***

Washed components are prepared by washing blood cells with 0.9% Sodium Chloride [Injection (USP) with or without small amounts of dextrose.] Washed components have reduced content of original plasma constituents and the hermetic seal of the components has been broken; therefore, shelf life is no more than 24 hours if stored at 1-6 C or 4 hours if stored at 20-24 C.

***Actions***

Washed components have therapeutic properties similar to the original component; there will be some loss of red cells, platelets, and platelet function.

***Indications***

Washed blood is indicated 1) if the plasma contains antibodies known to be harmful for the intended recipient or 2) to remove constituents to which the intended recipient is known to have severe side effects. These components are indicated for the removal of antibodies such as anti-IgA or anti-HPA-1. Washed blood is also indicated in rare recipients experiencing anaphylactoid reactions to plasma components.

***Contraindications***

Same as for original component. Washed components should not be considered leukocyte reduced.

***Dosage and Administration***

The same as for original component.

***Side Effects and Hazards***

Same as original component except febrile and allergic reactions may occur less frequently and there is an increased potential for microbial contamination. Otherwise, the side effects (including risk of transfusion-transmitted viral infection) are similar to those of the original component.

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## Summary Chart of Blood Components

Category	Major Indications	Action/Recipient Benefit	Not Indicated For	Special Precautions	Hazards	Rate of Infusion
Whole Blood	Symptomatic anemia with large volume deficit	Increases oxygen-carrying capacity Increases blood volume	Condition responsive to specific component Volume expansion Treatment of coagulopathy	Must be ABO identical	Infectious diseases Hemolytic, septic/toxic, allergic, febrile reactions Circulatory overload GVHD	For massive loss, as fast as patient can tolerate Must be infused within 4 hours
Whole Blood Irradiated	See Whole Blood, Risk for GVHD	See Whole Blood GVHD is reduced	See Whole Blood	See Whole Blood	See Whole Blood	See Whole Blood
Red Blood Cells; Red Blood Cells, (Adenine-Saline Added); Red Blood Cells, Low Volume; Red Blood Cells Apheresis	Symptomatic anemia	Increases oxygen carrying capacity	Pharmacologically treatable anemia Coagulation deficiency Volume expansion	Must be ABO-compatible	Infectious diseases Hemolytic, septic/toxic, allergic, febrile reactions GVHD	As patient can tolerate but less than 4 hours
Red Blood Cells Deglycerolyzed	See Red Blood Cells, IgA deficiency with anaphylactoid reactions	See Red Blood Cells Deglycerolization removes plasma protein Risk of allergic and febrile reactions reduced	See Red Blood Cells	See Red Blood Cells	See Red Blood Cells Hemolysis due to incomplete deglycerolization can occur	See Red Blood Cells
Red Blood Cells Irradiated	See Red Blood Cells, Risk for GVHD	See Red Blood Cells Gamma irradiation inactivates donor lymphocytes GVHD is reduced	See Red Blood Cells	See Red Blood Cells	See Red Blood Cells	See Red Blood Cells
Red Blood Cells Leukocytes Reduced	See Red Blood Cells Febrile reactions from leukocyte antibodies	See Red Blood Cells Reduction of leukocytes reduces risk of febrile reactions, HLA alloimmunization and CMV infection	See Red Blood Cells Leukocyte reduction should not be used to prevent GVHD	See Red Blood Cells	See Red Blood Cells If using bedside leukoreduction filter, hypotensive reaction may occur	See Red Blood Cells
Red Blood Cells Washed	See Red Blood Cells IgA deficiency with anaphylactoid reactions Recurrent severe allergic reactions to unwashed red blood cell products	See Red Blood Cells Washing reduces plasma proteins Risk of allergic reactions may be reduced	See Red Blood Cells	See Red Blood Cells	See Red Blood Cells	See Red Blood Cells

For all cellular components there is risk the recipient may become alloimmunized. RBC-containing components and thawed plasma should be stored at 1-6 C. Platelets, Granulocytes, and thawed Cryprecipitate should be stored at 20-24 C.

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**Summary Chart of Blood Components (continued)**

Fresh Frozen Plasma (FFP); FFP Donor Retested	Deficiency of labile and stable plasma coagulation factors and TTP	Source of deficient or defective plasma proteins	Volume replacement Coagulopathy that can be more effectively treated with specific therapy	Must be ABO-compatible	Infectious diseases Allergic reactions Circulatory overload	Less than 4 hours
Liquid Plasma; Plasma; Thawed Plasma; Plasma Frozen Within 24 Hours	Deficiency of stable coagulation factors	Source of nonlabile factors	See FFP Deficiency of Factors V and VIII:C or volume replacement	Must be ABO-compatible	See FFP	Less than 4 hours
Plasma Cryoprecipitate Reduced	TTP	See FFP Deficient in Factor I, VIII, vWF, and XIII Deficient in high molecular weight vWF multimers as compared to FFP	See FFP Deficiency of coagulation factors known to be depleted in this product, Factors I, VIII, vWF, XIII Volume replacement	Must be ABO-compatible	See FFP	Less than 4 hours
Cryoprecipitated AHF; Cryoprecipitated AHF, Pooled	Hemophilia A von Willebrand's disease Hypofibrinogenemia Factor XIII deficiency	Provides Factor VIII, fibrinogen, vWF, Factor XIII	Deficiency of any plasma protein other than those enriched in Cryoprecipitated AHF	Frequent repeat doses may be necessary	Infectious diseases Allergic reactions	Less than 4 hours
Platelets; Platelets Pooled	Bleeding from thrombocytopenia or platelet function abnormality	Improves hemostasis	Plasma coagulation deficits Some conditions with rapid platelet destruction (eg ITP,TTP) unless life threatening hemorrhage	Should not use some filters (check manufacturer's instructions) Should be ABO compatible with plasma	Infectious diseases Septic/toxic, allergic, febrile reactions GVHD	Less than 4 hours
Platelets, Pheresis	See Platelets	See Platelets May be HLA (or other antigen) selected	See Platelets	See Platelets	See Platelets	See Platelets
Platelets Irradiated; Platelets Pooled Irradiated; Platelets Pheresis Irradiated	See Platelets Risk of GVHD	See Platelets Gamma irradiation inactivates donor lymphocytes reduced risk of GVHD	See Platelets	See Platelets	See Platelets	See Platelets

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**Summary Chart of Blood Components (continued)**

Platelets Leukocytes Reduced; Platelets Pheresis Leukocytes Reduced	See Platelets Febrile reactions Prevention of HLA alloimmunization	See Platelets Reduction of leukocytes reduces risk of febrile reactions, HLA alloimmunization, and CMV	See Platelets Leukocyte reduction Should not be used to prevent GVHD	See Platelets	See Platelets	See Platelets
Granulocytes Pheresis, Granulocytes/ Platelets Pheresis	See Platelets Neutropenia with infection, unresponsive to appropriate antibiotics	Provides granulocytes with or without platelets	Infection responsive to antibiotics, eventual marrow recovery not expected	Must be ABO compatible Should not use some filters (check manufacturer's instructions)	Infectious diseases Allergic reactions Febrile reactions GVHD	One unit over 2-4 hours Closely observe for reactions
Granulocytes Pheresis Irradiated; Granulocytes Platelets Irradiated	See Granulocytes See Platelets	Provides granulocytes with or without platelets	See Granulocytes See Platelets	See Granulocytes See Platelets	See Granulocytes See Platelets	See Granulocytes See Platelets

For all cellular components there is risk the recipient may become alloimmunized. RBC-containing components and thawed plasma should be stored at 1-6 C. Platelets, Granulocytes, and thawed Cryprecipitate should be stored at 20-24 C.

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