

Guidance for Industry

An Acceptable Circular of Information for the Use of Human Blood and Blood Components

Draft Guidance

This guidance comment is being distributed for comment purposes only.

Submit comments and suggestions regarding this draft document by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance and the “Circular of Information for the Use of Human Blood and Blood Components” are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448 or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of the document, contact the Office of Blood Research and Review at 301-827-6178.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
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GUIDANCE FOR INDUSTRY

An Acceptable Circular of Information for the Use of Human Blood and Blood Components

This guidance document represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

The Food and Drug Administration (FDA) is recognizing as acceptable for use by manufacturers of blood and blood components intended for transfusion subject to United States statutes and regulations, the instruction circular entitled "Circular of Information for the Use of Human Blood and Blood Components" (Circular) dated July 2002. The July 2002 Circular provides specific labeling directions for the administration and use of blood and blood components intended for transfusion. The FDA, Center for Biologics Evaluation and Research (CBER), believes that the Circular will assist manufacturers in complying with labeling requirements under 21 CFR 606.122. The requirements under § 606.122 specify that an instruction circular must be available for distribution with blood and blood components intended for transfusion. Section 606.122 further specifies the information that is required in the instruction circular.

II. BACKGROUND

The Circular is prepared jointly by the American Association of Blood Banks (AABB), America's Blood Centers (ABC) and the American National Red Cross (ARC). The Circular is periodically updated to address changes in regulations, technology, testing, and product indications. Recently, AABB submitted to FDA a revised draft version of the Circular dated July 2002. This version updates the previous version dated August 2000. FDA has subsequently reviewed the submission and sent comments to AABB. AABB incorporated FDA's comments and submitted the final version to FDA in July 2002.

III. FDA REVIEW AND CONCLUSION

FDA has reviewed the final version of the Circular and finds it acceptable at this time for use in the labeling of blood and blood components intended for transfusion (§ 606.122). Manufacturers that have implemented licensed nucleic acid tests (NAT) may use this version of the Circular, which is dated July 2002. A copy of the Circular is found in section V. below. Those

manufacturers that have not yet implemented NAT may continue to use the August 2000 version of the Circular. Any subsequent modifications to the version of the Circular dated July 2002 by AABB, ABC, and ARC are not covered by this guidance.

IV. SUPPLEMENTARY INFORMATION

You may obtain the Circular dated July 2002 from:

American Association of Blood Banks
8101 Glenbrook Road
Bethesda, MD 20814-2749

Persons with access to the Internet may obtain the document at <http://www.aabb.org>.

The draft guidance document and the Circular may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800. Persons with access to the Internet may obtain the documents at <http://www.fda.gov/cber/guidelines.htm>.

A copy of the Circular is reproduced below.

V. THE CIRCULAR

Below is a copy of the “Circular of Information for the Use of Human Blood and Blood Components” dated July 2002:

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, and is recognized as acceptable by the Food and Drug Administration.



AMERICAN ASSOCIATION OF BLOOD BANKS



**America's Blood
Centers**



American Red Cross

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 for the Use of Human Blood and Blood Components* (hereafter referred to as *Circular*) is an extension of 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 patient treatment. 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 and variant Creutzfeldt-Jakob disease (vCJD) 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 cells and white 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 need for allogeneic transfusion with its attendant risks of disease transmission and immune reactions.

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 hepatitis and 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 provision 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 performed before units of blood or blood components are distributed 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), and nonreactive for hepatitis B surface antigen (HBsAg). Licensed nucleic acid tests (NAT) for HCV RNA and HIV-1 RNA have been performed and found to be nonreactive. A serologic test for syphilis has been performed and found to be nonreactive. Alanine aminotransferase (ALT) testing is no longer required to qualify blood for transfusion.

For units labeled for autologous use only, at a minimum the first donation from the donor-patient in each 30-day period is tested for evidence of infection as listed above. Subsequent units that are not tested will be labeled as "DONOR TESTED WITHIN THE LAST 30 DAYS." If an establishment allows any autologous donation to be used for allogeneic transfusion, or ships autologous donations to any establishment that does, the collecting establishment must test each donation for evidence of infection as listed above. This includes units labeled for autologous use only. Infectious disease testing for autologous units may be omitted for autologous units drawn, stored, and infused at the same facility. Autologous units for which testing has not been performed are labeled "DONOR UNTESTED." Autologous units with positive tests may be used for transfusion to the donor-patient with appropriate physician authorization. A biohazard label will be applied to autologous units that are tested for evidence of infection as listed above and determined to be positive.

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 clin-

ically 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 cytophoresis
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, if applicable.
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 designed to remove clots and aggregates (generally a standard 170- to 260-micron filter).
5. Blood and 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 with the exception of 0.9% Sodium Chloride, Injection (USP), unless a) they have been approved for this use by the FDA or b) there is documentation available to show that the addition is safe and does not adversely affect the blood or component.
7. Lactated Ringer's, Injection (USP) or other solutions containing calcium should never be added to or infused through the same tubing with blood or components 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 manner that violates the integrity of the system, 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.

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 its 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, and 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 ≥ 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; 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 symp-

omatic 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 (eg, 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 (see section on Testing of Donor Blood). 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, in-

- cluding 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.

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 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.

Components Containing Red Blood Cells

Whole Blood and Other Red-Cell-Containing Components

Description

Red cells contain hemoglobin and serve as the primary mechanism for transport of oxygen to 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 and those volumes are stated on the label.

Whole Blood can be stored for an interval ("shelf life") determined by the properties of the anticoagulant-preservative solution. Whole Blood units are prepared in a sterile manner in the empty container at a ratio of 14 mL per 100 mL whole blood collected. Actual collection volume may be $\pm 10\%$.

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 remain in these blood components and may cause adverse immunologic or physiologic conse-

Summary Chart of Anticoagulants

Anticoagulant/ Preservative	Trisodium Citrate	Citric Acid	Monobasic Sodium Phosphate	Dextrose	Adenine	Shelf Life
Anticoagulant Citrate Dextrose - A(ACD-A)	22.0 g/L	8.0 g/L	0	24.5 g/L	0	21 days
Citrate Phosphate Dextrose (CPD)	26.3 g/L	3.27 g/L	2.22 g/L	25.5 g/L	0	21 days
Citrate Phosphate Dextrose (CP2D)	26.3 g/L	3.27 g/L	2.22 g/L	51.1 g/L	0	21 days
Citrate Phosphate Dextrose Adenine (CPDA-1)	26.3 g/L	3.27 g/L	2.22 g/L	31.9 g/L	0.275 g/L	35 days

Note: Anticoagulant Citrate Dextrose is used as a preservative for apheresis components as recommended by the manufacturer.

quences. 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 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 are also indicated for exchange transfusion.

Contraindications

Red-cell-containing components should not be used to treat anemias that can be corrected with specific medications such as iron, vitamin B₁₂, folic acid, or erythropoietin.

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

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 can be made 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 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 performing ABO/Rh type, antibody screen, and crossmatching by serologic technique or use of electronic selection ("computer crossmatch").

The initial portion of each transfusion should be infused slowly, except in urgent situations, 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. (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.

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 (50-80 g of hemoglobin) suspended in varying quantities of residual plasma. Units of Whole Blood that are less than 405 mL (450 mL - 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 posttransfusion 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.

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 Donor lymphocytes are inactivated Risk of GVHD 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 Pheresis	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 fast as patient can tolerate but less than 4 hours

Red Blood Cells Deglycerolyzed	See Red Blood Cells IgA deficiency with anaphylactoid reaction	See Red Blood Cells Deglycerolization removes plasma proteins 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 Donor lymphocytes are inactivated Risk of GVHD 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 due to 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 leukocyte reduction filter, hypotensive reaction may occur	See Red Blood Cells

(cont'd)

Summary Chart of Blood Components (continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Red Blood Cells Washed	See Red Blood Cells IgA deficiency with anaphylatoid reaction Recurrent severe allergic reactions to unwashed red 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
Fresh Frozen Plasma (FFP); FFP Donor Re-tested	Deficiency of labile and stable plasma coagulation factors 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 coagulation factors	See FFP Deficiency of Factors V and VIII 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 coagu- lation factors known to be de- pleted in this prod- uct, 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 defi- ciency	Provides Factor VIII, fibrinogen, vWF, Factor XIII	Deficiency of any plasma protein other than those enriched in Cryoprecipitated AHF	Repeated doses may be necessary	Infectious diseases Allergic reactions	Less than 4 hours
Platelets; Platelets Pooled	Bleeding due to thrombocytopenia or platelet func- tion abnormality Prevention of bleed- ing from marrow hypoplasia	Improves hemostasis	Plasma coagulation deficits Some conditions with rapid platelet destruction (eg ITP, TTP) unless life threatening hemorrhage	Should not use some filters (check man- ufacturer's instruc- tions)	Infectious diseases Septic/toxic, aller- gic, febrile reaction GVHD	Less than 4 hours

(cont'd)

Summary Chart of Blood Components (continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
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
Platelets Leukocytes Reduced; Platelets Pheresis Leukocytes Reduced	See Platelets Prevention of febrile reactions Prevention of HLA alloimmunization	See Platelets Reduction of leukocytes reduces risk of febrile reactions, HLA alloimmunization, and CMV infection	See Platelets Leukocyte reduction should not be used to prevent GVHD	See Platelets	See Platelets	See Platelets

Granulocytes Pheresis; Granulo- cytes/Platelets Pheresis	See Platelets Neutropenia with infection, unre- sponsive to appro- priate antibiotics	Provides granulo- cytes with or with- out platelets	Infection responsive to antibiotics, eventual marrow recovery not ex- pected	Must be ABO com- patible Should not use some filters (check man- ufacturer's instruc- tions)	Infectious diseases Allergic reactions Febrile reactions GVHD	One unit over 2-4 hours Closely observe for reactions
Granulocytes Pheresis Irradiated, Granulocytes Plate- lets Irradiated	See Granulocytes See Platelets	Provides granulo- cytes with or with- out platelets Donor lymphocytes are inactivated	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.

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 CPD, CPDA-1, and AS-1 storage solutions 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 washed and transfused within 24 hours or 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 blood cells collected by apheresis. Aside from the automated collection method used, the component is comparable to red blood cells collected by manual phlebotomy in all aspects. 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 grams of hemoglobin per unit. For comparison, a typical unit of Red Blood Cells derived from a whole blood collection contains 50 to 80 grams of hemoglobin.
10. Any of the above may be **irradiated**. See section on Further Processing.

Plasma Components

Plasma Components Containing Functional Amounts of Labile Coagulation Factors (Factors V and VIII)

Description

Fresh Frozen Plasma (FFP) is prepared from a whole blood or apheresis collection and frozen at -18°C or colder within the time frame required for the anticoagulant or collection process. 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 of plasma proteins for patients who are deficient in or have 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 (eg, liver disease).
2. Patients with massive transfusion who have clinically significant coagulation deficiencies.
3. Patients on warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need to have anti-coagulation therapy after the procedure.
4. For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).
5. Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation 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 AHP, or Factor VIII 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 should be infused immediately or stored at 1-6 C for up to 24 hours. If stored greater than 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.

Specific Plasma Components

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. Such retesting is intended to reduce the risk of virus transmission from donors who may be in the infectious window period.

Plasma Components Containing Reduced Amounts of Labile Coagulation Factors

Description

Other plasma components may be made from whole blood collected in all approved anticoagulants 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 plasma proteins for patients who have defective or are deficient in plasma proteins, except for Factor V and Factor VIII.

Indications

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

Contraindications

Same as for FFP. Do not use Plasma, Thawed Plasma, or Liquid Plasma for replacement of coagulation Factors V and VIII.

Dosage and Administration

Same as for FFP.

Side Effects and Hazards

Same as for FFP.

Specific Plasma Components

1. **Thawed Plasma** (THAWED PLASMA) is derived from FFP prepared in a way that ensures sterility (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 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. Plasma, Cryoprecipitate Reduced can also be prepared from FFP Donor Retested.

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 for transfusion or plasma exchange in patients with TTP refractory to FFP. It may be used to provide clotting factors except Factor I (fibrinogen), Factor VIII, Factor XIII, and vWF.

Contraindications

This component should not be used as a substitute for FFP.

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)

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, Factor XIII, fibrinogen, vWF, and fibronectin. Each unit of Cryoprecipitated AHF should contain ≥ 80 IU Factor VIII units and ≥ 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 and 150 mg of fibrinogen for each unit of Cryoprecipitated AHF indicated on the label.

Action

Cryoprecipitate serves as a source of Factor VIII, fibrinogen, vWF, and Factor XIII.

Indications

This component is indicated as second-line therapy for von Willebrand disease and hemophilia A (Factor VIII deficiency). Coagulation factor preparations are the preferred components when blood component therapy is needed for management of von Willebrand disease and Factor VIII deficiency. **Cryoprecipitate should be used only if virus-inactivated Factor VIII concentrates or recombinant factor preparations are not available for management of patients with hemophilia A or von Willebrand 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). This component should not be given if there is evidence of container breakage or of thawing during storage. Do not refreeze 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 within 4 hours if it is an open system or units have been pooled.

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).

For treatment of bleeding in patients with hemophilia A, rapid infusion of a loading dose expected to produce the desired level of Factor VIII 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 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 turnover should be monitored with fibrinogen assays.

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

Number of bags of cryoprecipitate required =

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

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

*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 assays.

For treatment of von Willebrand 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 5.5×10^{10} platelets suspended in 40-70 mL of plasma, which contain normal levels of stable coagulation factors. Depending upon the technique used in prepa-

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

Actions

Platelets are essential for normal hemostasis. Complex reactions occur between platelets, von Willebrand factor, and collagen in the walls of disturbed vasculature, phospholipid, and soluble coagulation factors including thrombin. These changes induce platelet adherence to vessel walls and 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/ μ L) secondary to cancer, marrow aplasia, or chemotherapy. Platelet transfusion may also be useful in selected cases of postoperative bleeding, eg, platelet count less than 50,000/ μ L. If platelet function is normal, platelets should not be transfused if the platelet count is greater than 100,000/ μ 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 or transfused 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. Except in unusual circumstances, the donor plasma should be ABO compatible with the recipient's red cells when this component is to be transfused to infants or when large volumes are to be transfused. 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/ μ L and increase the count of an 18-kg child by 20,000/ μ L. The usual dose in an adult patient is 4-8 units. For prophylaxis, 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 calculated measure of patient response to platelet transfusion that adjusts for the number of platelets infused and the size of the recipient.

$$CCI = (\text{post-count} - \text{pre-count}) \times BSA / \text{platelets transfused}$$

where post-count and pre-count are platelet counts (/ μ L) after and before transfusion, respectively; BSA is the patient body surface area (meter²); and platelets transfused is the number of administered platelets ($\times 10^{11}$). For example:

A patient with acute myelogenous leukemia with a nomogram-derived body surface area of 1.40 meter² is transfused with a unit of Platelets Pheresis. The collecting facility label indicates a platelet dose of 4.5×10^{11} . The pre-transfusion platelet count is 2000/ μ L. The patient's platelet count from a sample of blood collected 15 minutes after platelet transfusion is 29,000/ μ L. The CCI is calculated as $(29,000 - 2,000) \times 1.4 / 4.5 = 8400$.

In the clinically stable patient, the CCI is typically greater than 7500 at 10 minutes to one hour after transfusion and remains above 4500 at 24 hours. Both immune and nonimmune mechanisms may contribute to reduced platelet recovery and survival. Along with supportive serologic test results, a CCI of lower than 5000 at 10 minutes to 1 hour after transfusion may indicate an immune-mediated refractory state to platelet therapy. With nonimmune mechanisms, platelet recovery within 1 hour may be adequate although survival at 24 hours is reduced. 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. 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 compo-

- nent(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, ie, 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 (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 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.

Components Available

1. **Platelets (PLATELETS)**
A unit of Platelets is a concentrate of platelets separated from a single unit of Whole Blood. One unit of Platelets should contain no fewer than 5.5×10^{10} platelets suspended in 40-70 mL of 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 5.5×10^{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. ACD-A is the anticoagulant solution currently used for the collection and preservation of Platelets Pheresis.

In patients refractory to platelets from unmatched donors, this component may be especially useful if selected to be HLA-matched or if determined recipient-compatible by serologic methods. Other causes of refractoriness to Platelets include 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 Leukocyte Reduced (PLATELETS, LEUKOCYTES REDUCED)**

Platelets and Platelets Pheresis can be prepared to be leukocyte reduced. Platelets and Platelets Pheresis may also be further processed using leukocyte reduction filters. These may be labeled Platelets Leukocytes Reduced or Platelets Pheresis Leukocytes Reduced provided that the residual leukocyte count is $< 8.3 \times 10^5$ or $< 5 \times 10^6$, respectively, and the platelet recovery is at least 85% of the prefiltration content. Alternatively, Platelets Pheresis may be collected to contain a therapeutic adult dose of platelets and very few leukocytes. If the leukocyte content is $< 5 \times 10^6$ and the platelet count is $> 3 \times 10^{11}$ platelets, the unit can be labeled Platelets Pheresis Leukocytes Reduced. The volume, anticoagulant/preservative, and storage conditions for leukocyte-reduced platelet components are the same as those for Platelets or Platelets Pheresis, respectively. Platelets Leukocytes Reduced or Platelets Pheresis Leukocytes Reduced are indicated to decrease the frequency of recurrent febrile, nonhemolytic transfusion reaction, HLA alloimmunization and transfusion-transmitted CMV infection (See section on Further Processing.)

Granulocyte Components

Description

Granulocyte transfusion therapy is controversial. Granulocyte concentrates are typically 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 donor administration of granulocyte colony-stimulating factor and/or corticosteroids. The final volume of the Granulocytes Pheresis product is 200-300 mL including anticoagulant and plasma as indicated on the label.

Red cell sedimenting agents approved by the FDA, such as hydroxyethyl starch (HES), are typically used in the collection of granulocytes. Residual agent will be present in the final component and is described on the 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 3×10^{11} platelets and 1×10^{10} granulocytes. Administration is the same as for Granulocytes Pheresis, since 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.

Indications

Granulocytes Pheresis is used typically in the treatment of neutropenic patients (generally less than $0.5 \times 10^9/L$ [$500/\mu L$]) in whom eventual marrow recovery is expected, who have documented infections (especially gram-negative bacteria and fungi), and who have not responded to antibiot-

ics. A trial of broad-spectrum antimicrobial agents should be used before granulocyte transfusion therapy is initiated. If the intended recipient is CMV-seronegative and severely immunosuppressed (eg, a marrow transplant recipient), CMV-seropositive granulocytes should not be given. In addition to neutropenic patients, patients with hereditary neutrophil function defects (such as chronic granulomatous disease) may be candidates to receive granulocyte transfusion therapy. Prophylactic use of granulocytes in non-infected patients is not recommended.

Dosage and Administration

Transfuse as soon as possible. A standard blood infusion set is to be used for the administration of Granulocytes Pheresis because depth-type microaggregate filters and leukocyte reduction filters remove granulocytes. The red cells in Granulocytes Pheresis must be ABO-compatible with the recipient's antibodies. 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.

Because most patients receiving these products are severely immunosuppressed, Granulocytes Pheresis should be 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 recipient medication such as 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. One or more of these processes may be performed on a component.

Leukocyte Reduction

Examples of 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 reduction may be achieved by in-process collection or filtration: 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 may not be quality controlled. 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. The leukocyte-reduced component will have therapeutic efficacy equal to at least 85% of the original component. Currently, washing is not a substitute for leukocyte reduction and leukocyte reduction is not a substitute for irradiation.

Indications

Leukocyte-reduced components are indicated to decrease the frequency of recurrent febrile nonhemolytic 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

Leukocyte-reduced components do not prevent GVHD. Leukocyte reduction filters are not to be used in the administration of Granulocytes Pheresis.

Side Effects and Hazards

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.

Further Testing to Identify CMV-Seronegative Blood

Description

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

Indications

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

Irradiation

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 irradiation. The standard dose of gamma irradiation is 2500 cGy targeted to the central portion of the container with a minimum dose of 1500 cGy delivered to all other parts of the component. Maximum allowable dose is 5000 cGy.

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.

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.

Washing

Examples of Washed Components:

Red Blood Cells Washed (WASHED RED BLOOD CELLS)

Platelets Washed (WASHED PLATELETS)

Platelets Pheresis Washed (WASHED APHERESIS PLATELETS)

Description

Washed components are typically prepared using 0.9% Sodium Chloride, Injection (USP) with or without small amounts of dextrose. Washing removes unwanted plasma proteins, including antibodies. There will also be some loss of red cells and platelets, as well as a loss of platelet function through platelet activation. The hermetic seal of the components has been broken, therefore, shelf life is no more than 24 hours at 1-6 C or 4 hours at 20-24 C. Washing is not a substitute for leukocyte reduction.

Indications

Washing of blood components is indicated to remove unwanted plasma when it contains constituents that predispose patients to significant transfusion reactions, eg, the removal of IgA-containing plasma in providing transfusion support for an IgA-deficient recipient or in rare recipients experiencing anaphylactoid reactions to plasma components.

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