A Compendium of Transfusion Practice Guidelines
Authors:
Ralph Vassallo, MD, FACP, Chair

Gary Bachowski, MD, PhD, North Central Region
Richard J. Benjamin, MD, PhD, National Headquarters
Dayand Borge, MD PhD, Greater Chesapeake and Potomac Region
Roger Dodd, PhD, National Headquarters
Anne Eder, MD, PhD, National Headquarters
Paul J. Eastvold, MD, MT (ASCP), Lewis and Clark Region
Corinne Goldberg, MD, Carolinas Region
Courtney K. Hopkins, DO, South Carolina Region
José Lima, MD, Southern Region
Lisa G.S. McLaughlin, MD, JD, National Headquarters
Yvette Marie Miller, MD, Donor and Client Support Center
Patricia Pisciotto, MD, Connecticut Region
Salima Shaikh, North Central Region
Susan Stramer, PhD, National Headquarters
James Westra, MD, Northern Ohio Region

Editor:
Ralph Vassallo, MD, FACP

Prior Edition Editors:
NurJehan Quraishy, MD
Linda Chambers, MD
Yvette Miller, MD

Production Editor
Liz Marcus, National Headquarters
Users of this brochure should refer to the Circular of Information for blood and blood products regarding the approved indications, contraindications, and risks of transfusion, and for additional descriptions of blood components.

Copies of the Circular of Information can be obtained from your American Red Cross Blood Services region or the AABB (aabb.org). The complete text of the side effects and hazards of blood transfusion from the current Circular of Information appears in the appendix section of the brochure.

Users must also refer to the current Circular of Information and AABB Standards for regulatory requirements.
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Introduction

The art of transfusion has historically been based on personal experience, local practice, expert opinion, and consensus conference recommendations, frequently without a sound foundation in evidence-based medicine. Increasingly, the assumptions and practices of the past are being challenged by improvements in hemovigilance data that document the adverse effects of transfusion, randomized controlled trials (RCTs) demonstrating both the benefits and risks of transfusion, and growing debates regarding alternate therapies. The concepts of patient-centered blood management (PBM) have emerged as a major force in the industry, with their focus on preventing the need for transfusion whenever possible.

Transfusion used to treat bleeding and/or medical conditions that cause anemia is now recognized as an important correlate of poor patient outcomes. The onus is on hospitals to optimize patients’ baseline condition prior to surgery, to minimize surgical and other sources of blood loss resulting in allogeneic transfusion and to harness patients’ physiological tolerance of anemia. The message that blood transfusion is lifesaving when used appropriately and dangerous if abused is being delivered to ordering physicians on an unprecedented scale.

Optimum patient care and PBM principles require that the medical staff agree to a set of practice guidelines for ordering and administering blood products. Practice guidelines now can be grounded in well-designed clinical trials that
clearly establish the safety, and in some cases superiority, of restrictive red cell transfusion practices. The need for platelet and plasma transfusions is also increasingly defined by randomized controlled studies that support conservative use. The National Blood Collection and Utilization Surveys documented a dramatic 8% drop in U.S. red cell transfusions between 2008 and 2011; however, variability in transfusion practice between and within hospitals is still common, often reflecting hospital tradition as well as local and community practice. National and local practice guidelines are a powerful tool to minimize this variation and optimize clinical practice.

The importance of optimum transfusion practice is now under the purview of accrediting and regulatory agencies. Blood transfusion is acknowledged to be a therapy that involves risks, so that each organization’s performance monitoring and improvement program must address the use of blood and blood components, requiring that hospitals institute a cross-functional group of medical and support staff charged with the responsibility of oversight. Transfusion-related fatalities and ABO-incompatible transfusions have long been reportable sentinel events; however, the Joint Commission has seen the need to promulgate a set of voluntary PBM performance measures that are likely the prelude to accreditation standards in the future.
Introduction

This compendium is a review of the current blood usage guidelines published in English in peer-reviewed journals. Whenever possible, RCTs are included, but where lacking, the discussion is informed by expert panels and retrospective cohort studies. We have, when possible, avoided single institution studies and controversial retrospective studies whose analysis and conclusions appear to be confounded, until prospective RCT data are available (for example, fresh versus old blood). The authors, all of whom are physician staff for the American Red Cross, have made every attempt to fairly reproduce the advice and lessons contained in these publications. They hope that this brochure will be a valuable resource to hospital staff who obtain blood and blood components from the Red Cross as they develop and update their blood usage guidelines to help improve patient care.
Components

Approved name: Red Blood Cells.

Also referred to as packed cells, red cells, packed red blood cells, RBCs.

Whole blood is rarely required and is, therefore, not addressed.

Description of Components

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

Depending on the preservative-anticoagulant system used, the hematocrit (Hct) of RBCs is ~55–65% (for example, Additive Solution [AS]-1, AS-3, AS-5, AS-7) to ~65–80% (for example, citrate-phosphate-dextrose-adenine solution [CPDA]-1, CPD, CP2D). RBCs contain 20–100 mL of donor plasma, generally <50 mL, in addition to the preservative and anticoagulant solution. The typical volume of AS RBCs after addition of the additive solution is 300–400 mL.

Each unit contains approximately 50–80 g of hemoglobin (Hgb) or 160–275 mL of pure red cells, depending on the
Hgb level of the donor, the starting whole blood collection volume, and the collection methodology or further processing. When leukoreduced, RBC units must retain at least 85% of the red cells in the original component.

Each unit of RBCs contains approximately 250 mg of iron, mostly in the form of Hgb.

**Selection and Preparation**

RBCs must be compatible with ABO antibodies present in the recipient plasma and must be crossmatched (serologically or electronically, as applicable) to confirm compatibility with ABO and other clinically significant antibodies prior to routine transfusion. Units must be negative for the corresponding antigens.

Rh-positive units may be transfused in an emergency to Rh-negative males and females with non-childbearing potential who have not made anti-D or whose D antigen type is unknown. The D-negative frequency is 17% in U.S. Caucasians, 7% in African-Americans and 2% in Asians. While the incidence of anti-D production in Rh-negative healthy volunteers is >80%, the incidence of anti-D production after transfusion of Rh-positive blood to Rh-negative hospitalized individuals is ~20–30%.

Transfusion services should develop policies on using Rh-positive blood in Rh-negative individuals to conserve Rh-negative units for Rh-negative females of child-bearing potential who are Rh-negative or Rh-unknown, recipients with anti-D, and those on chronic transfusion protocols when inventory of Rh-negative units is limited. This may include
switching to Rh-positive units in males and females with non-childbearing potential.\textsuperscript{8}

Extended storage preservative-anticoagulant preparations, such as AS-1 and AS-3, are appropriate for nearly all patients and extend the shelf-life of RBCs to 42 days. Physicians concerned about preservative-anticoagulant from large volume transfusions in neonates may elect to remove preservative-anticoagulant from transfusion aliquots prior to administration—for example, by centrifugation and volume reduction or washing.\textsuperscript{9}

Large randomized controlled trials are ongoing to study the clinical outcomes of RBC transfusion at variable storage lengths.\textsuperscript{10,11} A prospective, randomized controlled trial in premature infants weighing <1,250g did not demonstrate improved outcomes in patients who received fresh RBCs (< 7 days old) versus standard blood bank practice (mean age of RBCs at transfusion 14.6 days).\textsuperscript{12}

RBCs are capable of transmitting cytomegalovirus, mediating graft-versus-host disease, and causing febrile nonhemolytic transfusion reactions. For recipients at particular risk from these transfusion-related complications, use of CMV reduced-risk (that is, CMV-seronegative or leukocyte-reduced), irradiated, and leukoreduced preparations, respectively, should be considered.

**Dosing**

RBCs should be transfused based on clinical need.

In the absence of acute hemorrhage, RBC transfusion should be given as single units.\textsuperscript{8,15}
Transfusion of a unit of RBCs should be completed within four hours. Smaller aliquots of the unit can be prepared if the time for transfusion will exceed four hours.

**Response**

In a stable, non-bleeding or hemolyzing adult transfused with compatible RBCs:

- Hemoglobin (Hgb) equilibrates in 15 minutes after RBC transfusion.\(^{13}\)

- One unit will increase the Hgb level in an average-sized individual by approximately 1 g/dL and the Hct by 3%.\(^{13}\)

- The posttransfusion Hct can be accurately predicted from the patient’s estimated blood volume, baseline red cell volume (blood volume X venous Hct X 0.91), and transfused volume of red cells (unit volume x unit Hct).

In neonates, a dose of 10–15 mL/kg is generally given, and additive solution red cells with an Hct of approximately 60% will increase the Hgb by about 3 g/dL.

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

**Indications and Contraindications**

RBCs are indicated for patients with a symptomatic deficiency of oxygen-carrying capacity or tissue hypoxia due to an inadequate circulating red cell mass. They are also indicated for exchange transfusion (for example, for hemolytic disease of the fetus and newborn) and red cell exchange (for example, for acute chest syndrome in sickle cell disease).
Patients must be evaluated individually to determine the proper transfusion therapy, with care taken to avoid inappropriate over- or under-transfusion. Transfusion decisions should be based on clinical assessment as well as hemoglobin level.  

RBCs may be used for patients with acute blood loss that is refractory to crystalloid infusions. RBCs should not be used to treat anemia that can be corrected with a non-transfusion therapy (for example, iron therapy or erythropoietin). They also should not be used as a source of blood volume, to increase oncotic pressure, to improve wound healing, or to improve a person’s sense of well-being.  

_For side effects and hazards, see Appendix 1._
Perioperative/Periprocedural

The function of an RBC transfusion is to augment oxygen delivery to tissues. Hemoglobin levels during active bleeding are imprecise measures of tissue oxygenation. Intravenous fluid resuscitation and the time needed for equilibration can significantly alter the measured hemoglobin concentration.\textsuperscript{17} In addition, a number of factors must be considered besides the blood Hgb level, such as oxygenation in the lungs, blood flow, Hgb oxygen affinity and tissue demands for oxygen.\textsuperscript{14,15,17} The Hgb level and clinical status of the patient should both be used in assessing the need for RBC transfusion.

The adequacy of oxygen delivery must be assessed in individual patients, particularly in patients with limited cardiac reserve or significant atherosclerotic vascular disease. If available, mixed venous O\textsubscript{2} levels, O\textsubscript{2} extraction ratios, or changes in oxygen consumption may be helpful in assessing tissue oxygenation.\textsuperscript{14,17} Other factors to consider, in addition to the above, include anticipated degree and rate of blood loss, and the effect of body temperature or drugs/anesthetics on oxygen consumption.\textsuperscript{14,17} Notwithstanding the above, the American Society of Anesthesiologists Task Force recommends the following:\textsuperscript{14}

- RBCs should usually be administered when the Hgb concentration is low (for example, <6 g/dL in a young, healthy patient), especially when the anemia is acute. RBCs

Red Blood Cells | Utilization Guidelines
are usually unnecessary when the Hgb concentration is >10 g/dL. These guidelines may be altered in the presence of anticipated blood loss.

- The determination of whether intermediate Hgb concentrations (that is, 6–10 g/dL) justify or require RBC transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.

The AABB Clinical Practice Guideline recommends considering transfusion in post-operative surgical patients for Hgb <8 g/dL or when clinically significant symptoms of anemia are present (for example, tachycardia unresponsive to fluid resuscitation).

Preoperative assessment and efforts to reduce the RBC transfusion requirement in the perioperative period include the evaluation and treatment of anemia prior to surgery and the evaluation for possible discontinuation or replacement of anticoagulant and antiplatelet medications (for example, aspirin) for a sufficient time prior to surgery in consultation with the prescribing physician. The use of alternative measures to reduce allogeneic red blood cell use should be considered, including intraoperative and postoperative autologous blood recovery, acute normovolemic hemodilution, and operative and pharmacologic measures that reduce blood loss. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines for patients
undergoing cardiothoracic surgery recommend a preoperative assessment to identify patients at elevated risk of bleeding and subsequent blood transfusions (advanced age, decreased preoperative red blood cell volume, and emergent or complex procedures), effective treatment of preoperative anemia, and the need for minimization of hemodilution during cardiopulmonary bypass (CPB) to preserve red blood cell volume. Additional recommendations of these guidelines include the appropriate management of preoperative antiplatelet and anticoagulant drug therapy, and the use of epsilon-aminocaproic acid or tranexamic acid to reduce total blood loss.

**General Critical Care**

The same considerations regarding individualization of red cell transfusions apply to critical care as well as to perioperative patients (see above). The effects of anemia must be separated from those of hypovolemia, although both can impede tissue oxygen delivery. Blood loss of greater than 30% of blood volume generally causes significant clinical symptoms; but in young, healthy patients, resuscitation with crystalloid alone is usually successful with blood loss of up to 40% of blood volume (for example, 2 liters blood loss in an average adult male). Beyond that level of acute blood loss, even after adequate volume resuscitation, acute normovolemic anemia will exist. However, oxygen delivery in healthy adults is maintained with Hgb levels even as low as 6–7 g/dL. Consider RBC transfusion in critically ill trauma patients after the immediate resuscitation phase if the Hgb level is <7 g/dL. Tranexamic acid can be used as an adjunct. RBC transfusion is indicated in patients with evidence of hemorrhagic shock and should be considered in patients with Hgb <7 g/dL who are on mechanical ventilation.
A restrictive RBC transfusion strategy (Hgb 7–8 g/dL trigger) is recommended in stable hospitalized patients.\textsuperscript{16} There are several prospective studies demonstrating a higher mortality rate in patients receiving RBCs than in those not receiving RBCs.\textsuperscript{20–22} The TRICC (Transfusion Requirements in Critical Care) trial, a multicenter, randomized, controlled trial compared a transfusion trigger of 7 g/dL with a trigger of 9 g/dL in normovolemic critically ill patients.\textsuperscript{21} Overall, 30-day mortality was similar in the two groups and in the subset of more seriously ill patients, but the restrictive group received significantly fewer RBC transfusions. However, in less acutely ill or younger patients, the restrictive strategy resulted in lower 30-day mortality while decreasing RBC transfusions.

There are limited clinical data evaluating Hgb levels for RBC transfusions in patients with or at significant risk for underlying cardiovascular disease.\textsuperscript{27} The AABB Clinical Practice Guideline suggests a restrictive transfusion strategy for hospitalized patients with underlying cardiovascular disease, with transfusion considered at Hgb <8 g/dL or when clinically significant symptomatic anemia is present.\textsuperscript{16} There is still some uncertainty regarding the risk of perioperative myocardial infarction with a restrictive versus liberal transfusion strategy in this setting.\textsuperscript{16}

In general, RBC transfusions may be beneficial in patients with acute coronary syndromes (unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction). However, there are few data evaluating the appropriate Hgb level in patients with ACS and the AABB Clinical Practice Guidelines could not recommend for or against a liberal or restrictive RBC transfusion threshold in this population.\textsuperscript{16}
A prospective, randomized controlled trial comparing a liberal transfusion strategy (Hgb 9 g/dL threshold) to a conservative transfusion strategy (Hgb 7g/dL threshold) in patients with acute upper gastrointestinal bleeding demonstrated reduced mortality at 45 days and decreased rate of further bleeding with the restrictive strategy, predominantly in patients with cirrhosis and Child-Pugh class A or B liver disease.24

Thus, transfusion triggers for red cells in critical care must be customized to defined patient groups, and the decision to transfuse must be based on individual patient characteristics. Unfortunately, the availability of carefully performed clinical trials to assist the clinician is limited.

**Pediatrics Critical Care**

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

The American Academy of Pediatrics has published guidance on specific indications for exchange transfusion for newborn infants at 35 or more weeks of gestation with hyperbilirubinemia, including that caused by HDFN.28 Infants with jaundice caused by HDFN are at greater risk of bilirubin encephalopathy and are treated more intensively than infants with “physiologic” jaundice at any given serum unconjugated bilirubin concentration.

Apart from HDFN, neonatal anemia occurs in many preterm infants because of iatrogenic blood loss for laboratory tests, concurrent infection or illness, and inadequate hematopoiesis in the first weeks of life. Transfusion thresholds for preterm infants and critically ill children have been widely debated
for years, but recent randomized studies support the use of a restrictive strategy (for example, transfusion at lower Hgb thresholds) compared to more liberal criteria (for example, transfusion at higher Hgb thresholds).29–31

In the multicenter PINT (Premature Infants in Need of Transfusion) study, 451 very low birth-weight infants were randomly assigned to receive red cell transfusions by either restrictive or liberal criteria. Infants in the restrictive transfusion group had lower mean Hgb values than those in the liberal group, and more infants avoided transfusion completely in the restrictive group (11%) compared to the liberal group (5%).31 There was no difference between the two groups in the composite outcome (death, severe retinopathy, bronchopulmonary dysplasia, and brain injury), supporting the use of restrictive transfusion criteria. In a smaller, single-center trial, Bell et al. randomized 100 preterm infants to either restrictive or liberal transfusion criteria and found a reduction in the number of transfusions in the restrictive group.29–30 However, infants in the restrictive group were noted as having more apnea episodes and neurologic events than infants in the liberal group. In conclusion, the documented benefits of restrictive transfusion practice are a decrease in the number of transfusions and exposure to fewer RBC donors, if a limited-donor program is not used. It is possible that the higher Hgb values maintained in the liberal transfusion group in the study of Bell et al. compared with the corresponding group in the PINT trial may have decreased the risk of apnea and brain injury.

A recent meta-analysis of clinical trials comparing outcomes between the use of restrictive versus liberal target hematocrit thresholds in neonates suggested that transfusion thresholds
can be lowered, but identified the need for additional clinical studies to clarify the impact of transfusion practice on long-term outcome. General guidelines for transfusion must take into consideration infants’ cardiorespiratory status, but transfusion decisions must be tailored to the individual patient.

**General Guidelines for Small-Volume (10–15 mL/kg) Transfusion to Infants**

<table>
<thead>
<tr>
<th>Maintain Hct between:</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>40–45%</strong></td>
<td>Severe cardiopulmonary disease* (for example, mechanical ventilation &gt;0.35 FiO₂)</td>
</tr>
<tr>
<td><strong>30–35%</strong></td>
<td>Moderate cardiopulmonary disease (for example, less intensive assisted ventilation, such as nasal CPAP or supplemental oxygen)</td>
</tr>
<tr>
<td><strong>30–35%</strong></td>
<td>Major surgery</td>
</tr>
<tr>
<td><strong>20–30%</strong></td>
<td>Stable anemia, especially if unexplained breathing disorder or unexplained poor growth</td>
</tr>
</tbody>
</table>

*Must be defined by institution.

**Chronic Anemia**

**Asymptomatic Chronic Anemia**

Treat with pharmacologic agents based on the specific diagnosis (for example, vitamin B₁₂, folic acid, erythropoietin, iron).

**Symptomatic Chronic Anemia**

Transfuse to minimize symptoms and risks associated with anemia. Transfusion is usually required when Hgb is <6 g/dL.
Anemia in Patients Receiving or Awaiting Chemo- or Radiotherapy

A large proportion (30–90%) of all cancer patients experience anemia associated either with the disease itself or with the cancer treatment regimen. Anemia (defined as Hgb <11 g/dL) has been shown to have an effect on tumor hypoxemia and thus on the tumor’s response to chemotherapy or radiotherapy, as well as on the quality of life for the patient. However, in general, Hgb levels >12 g/dL are also associated with increased morbidity and mortality. Meta-analyses of recent clinical studies indicate that the transfusion triggers differ, depending upon the type of cancer being treated; thus the Hgb goals are cancer-specific. Patients’ needs should be evaluated in light of the institution’s oncology guidelines.

Sickle Cell Disease

Evidence-based clinical guidelines and consensus statements have outlined indications for transfusion in sickle cell disease (SCD). SCD patients should be transfused with leukocyte-reduced blood. The antigenic phenotype of the red cells (at least ABO, Rh, Kell, Duffy, Kidd, Lewis, Lutheran, P, and MNS groups) should be determined in all patients older than 6 months. Alloimmunization and hemolytic transfusion reactions can be reduced by typing the patient for Rh and Kell blood group antigens to avoid transfusion of cells with these antigens (particularly E, C, and K) if the patient lacks them, and more extensive antigen matching in patients who are already alloimmunized. The choice between simple transfusion and exchange transfusion is often based on clinical judgment and available resources, with few clinical studies to guide decisions.
In preparation for surgery requiring general anesthesia, however, simple transfusion to increase Hgb to 10 g/dL was as effective as exchange transfusion in preventing perioperative complications in patients with sickle cell anemia and was associated with less blood usage and a lower rate of red cell alloimmunization.\(^{34,39}\)

Chronic transfusion therapy to maintain the HbS below 30% of the total Hgb prevents first stroke in high-risk children with abnormal transcranial Doppler studies and prevents recurrent stroke in those with a history of infarctive stroke.\(^{35–37,40}\) The treatment goal for prevention of recurrent stroke may be relaxed to less than 50% HbS after several complication-free years, but treatment cannot be safely discontinued at any point.\(^{35–37}\) Similarly, prophylactic transfusion cannot be safely discontinued in children with sickle cell anemia who have abnormalities on transcranial Doppler studies and are at a high risk of stroke (STOP 2, Stroke Prevention Trial in Sickle Cell Anemia).\(^{35–37,40}\) In contrast to simple transfusion, exchange transfusion can prevent iron accumulation and may reverse iron overload in chronically transfused patients.\(^{38}\)

In general, patients with SCD should not be transfused to a Hgb level >10 g/dL.
Accepted Indications for Transfusion in Sickle Cell Disease\textsuperscript{35}

<table>
<thead>
<tr>
<th>Episodic or Acute Complications of SCD</th>
<th>Chronic Complications of SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe anemia</td>
<td>Prevention of stroke in children with abnormal transcranial Doppler studies\textsuperscript{*}</td>
</tr>
<tr>
<td>Acute splenic sequestration</td>
<td>Prevention of stroke recurrence\textsuperscript{*}</td>
</tr>
<tr>
<td>Transient red cell aplasia</td>
<td>Chronic debilitating pain</td>
</tr>
<tr>
<td>Preparation for general anesthesia</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Sudden severe illness\textsuperscript{*}</td>
<td>Anemia associated with chronic renal failure</td>
</tr>
<tr>
<td>Acute chest syndrome\textsuperscript{*}</td>
<td></td>
</tr>
<tr>
<td>Stroke\textsuperscript{*}</td>
<td></td>
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<tr>
<td>Acute multiorgan failure\textsuperscript{*}</td>
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</tbody>
</table>

\textsuperscript{*}May be managed with simple transfusion or exchange transfusion

Controversial Indications\textsuperscript{35}

- Priapism
- Leg ulcers
- Pregnancy
- Preparation for infusion of contrast media
- “Silent” cerebral infarct and/or neurocognitive damage

Inappropriate Indications and Contraindications\textsuperscript{34}

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

**Severe Thalassemia**

Transfuse to help prevent symptomatic anemia and to suppress endogenous erythropoiesis by maintaining Hgb at 9–10 g/dL.\(^9\)
Components

Approved names: Apheresis Platelets, Apheresis Platelets Platelet Additive Solution Added Leukocyte Reduced, Platelets, Pooled Platelets.

Apheresis Platelets are also referred to as single donor platelets, or SDPs.

Platelets are also referred to as whole blood-derived platelets, random donor platelets, randoms, or RDPs. Pooled Platelets Leukocyte Reduced are referred to as Prestorage Pooled Platelets when pooled using a system FDA-cleared for up to five days of storage.

Description of Components

Apheresis Platelets (SDPs): obtained using automated instrumentation; should contain $\geq 3.0 \times 10^{11}$ platelets (generally $3.5-4.0 \times 10^{11}$) per bag in approximately 100–500 mL of plasma or plasma plus additive solution, dependent upon platelet yield and concentration. Anticoagulant is ACD.

Platelets (RDPs): derived from whole blood; should contain $\geq 5.5 \times 10^{10}$ platelets (average content approximately $8.5 \times 10^{10}$) per bag in 40–70 mL of plasma. Anticoagulant is the same as that used for whole blood collection, usually CPD.
or CP2D. Prestorage Pooled Platelets should contain ($\geq 5.5 \times 10^{10}$ platelets) x number of RDPs in the pool (usually 4–6).

*Leukoreduction standards are discussed in Blood Component Modifications.*

**Selection and Preparation**

Four to six RDPs are pooled at the blood center (prestorage pools) or at the hospital (poststorage pools) prior to transfusion to prepare an adult dose. Prestorage Pooled Platelets Leukocyte Reduced, and Apheresis Platelets/Apheresis Platelets Leukocyte Reduced are ready for transfusion.

Donor plasma should be ABO-compatible with the recipient's red cells when transfusing infants or large volumes to adults to avoid the possibility of hemolysis.

Rh-negative recipients should receive Rh-negative platelets when possible, particularly in women with childbearing potential. Consider administering Rh immune globulin if Rh-positive platelets need to be administered, especially when whole blood-derived platelets are used. Apheresis Platelets contain minimal quantities of red cells, but they are usually insufficient to provoke an alloimmune response in immunosuppressed patients.

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

To treat bleeding or prepare patients for invasive procedures, transfuse as needed to maintain the target platelet count. Four to ten units of RDPs, one to two units of Prestorage Pooled Platelets, or one to two SDPs are generally transfused to thrombocytopenic or thrombocytopathic adults. Prophylaxis at prespecified triggers may be accomplished with equivalent effect on hemorrhage, using three RDPs or half of an SDP in adults, albeit at the expense of more frequent (i.e., daily) administration provided that the minimum dose exceeds $1.1 \times 10^{11}$ platelets per square meter of patient’s body surface area.

Response

Measure platelet count from 10–60 minutes after transfusion. Generally, expect an average-sized adult (70 kg) platelet count increment of approximately 5,000–10,000/μL for each RDP given, or 10,000–60,000/μL for each SDP given. In neonates and infants, a dose of 5–10 mL/kg of RDPs should result in a 50,000–100,000/μL increment. A dose of 10 mL/kg is most often used. Similar dosing regimens have been used with SDP aliquots.

Approximately 7,100 platelets/μL are consumed daily in endothelial support functions, the equivalent of approximately one RDP per day for a 70 kg adult with marrow failure.

Platelet increments may be somewhat higher with ABO-identical or plasma-incompatible [group O donor → A recipient] versus platelet-incompatible units and with SDPs versus RDPs. Response to platelet transfusion is adversely affected by the presence of fever, sepsis, splenomegaly,
severe bleeding, consumptive coagulopathy, HLA alloimmunization, and treatment with certain drugs (for example, amphotericin B).49

**Indications and Contraindications**

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

Use prophylactically to prevent bleeding at prespecified low platelet counts. In general, maintain platelet count at >10,000/μL in stable, non-bleeding patients, at >20,000/μL in unstable, non-bleeding patients, and at >50,000/μL in patients who are actively bleeding or undergoing major invasive procedures/surgery. The avoidance of low hematocrits ameliorates uremic bleeding and may reduce the risk of hemorrhage in patients with thrombocytopenia.50

Use in patients with autoimmune thrombocytopenia, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, or heparin-induced thrombocytopenia with thrombosis should be avoided except for life-threatening hemorrhage. Use before invasive procedures/surgery in patients without thrombotic manifestations may be considered when the risk of bleeding is high.51,52

For side effects and hazards, see Appendix 1.
Cardiothoracic Surgery

- When coagulation parameters are not significantly abnormal, counts <100,000/µL accompanied by significant unexpected microvascular bleeding are appropriately treated with platelet transfusion.
- Routine prophylactic transfusions do not alter bleeding or postoperative transfusion requirements and are not recommended, even in patients on aspirin and P2Y₁₂ receptor inhibitors (for example, clopidogrel, prasugrel and ticagrelor), who are known to be at higher risk for bleeding and reoperation.⁶⁹

Point of care (POC) testing devices which reflect the availability of functional platelets and/or coagulation and fibrinolysis proteins are available to better assess hemostatic function in bleeding surgical patients. These tests can guide optimal administration of blood products and reduce inappropriate component utilization.⁶⁵–⁶⁷

Other Surgical Procedures

- Intraoperative platelet counts should be obtained to guide transfusion. Microvascular bleeding in the setting of potential dilutional thrombocytopenia may require empiric transfusion before counts are available.
- Prophylactic preoperative transfusion is rarely required for counts >100,000/µL, is usually required for counts <50,000/µL, and is guided by risk factors for intermediate counts.¹⁴
• Procedures with insignificant blood loss or vaginal deliveries can be performed at counts < 50,000/μL without prophylactic transfusion.
• Neurologic or ophthalmologic procedures may require a platelet count near 100,000/μL. 44
• Transfusion may be required with apparently adequate counts when known or suspected platelet dysfunction results in microvascular bleeding.

Specific Procedures

• When pre-procedural transfusion is deemed necessary, a posttransfusion count should be obtained to assure an appropriate increment before performance of the procedure.
• In the absence of coagulopathy or thrombocytopenia, major invasive procedures require functional platelet counts of at least 40,000–50,000/μL (including paracentesis/thoracentesis, respiratory tract/gastrointestinal [GI] biopsies, closed liver biopsy, sinus aspiration, and dental extraction).
• A threshold of 50,000/μL is often recommended for central venous catheter placement. At least one guideline, based on a more recent retrospective study and studies demonstrating improved safety with radiologic guidance suggests that a 20,000/μL threshold may be adequate. 63, 68
• Similarly, while many guidelines recommend a threshold of 50,000/μL, newer ones reserve this threshold for elective or high-risk lumbar puncture, noting potential safety for experienced operators at counts above 20,000/μL. 25, 53, 54
• A threshold of 80,000/μL has been proposed for spinal and epidural anesthesia. 56
- Fiberoptic bronchoscopy or GI endoscopy without biopsy may be safely performed by experienced operators in the presence of a platelet count <20,000/μL.⁵⁴,⁶³
- Bone marrow biopsy may be safely performed with counts at or below 10,000–20,000/μL.⁴⁴,⁵⁴,⁶³

**Platelet Function Defects**

Patients with congenital or acquired defects in platelet function may be transfused for critical bleeding or before major surgery regardless of the platelet count. Transfusion is generally not indicated when platelet dysfunction is extrinsic to the platelet (for example, uremia, certain subtypes of von Willebrand disease, hyperglobulinemia) since transfused platelets function no better than the patient’s own platelets. Other alternatives (for example, desmopressin in uremia or plasma exchange with hyperglobulinemia) are more often efficacious. When platelet surface glycoproteins are missing (for example, with Glanzmann thrombasthenia, Bernard-Soulier syndrome), transfusion should be undertaken only when more conservative efforts to manage bleeding have failed since alloimmunization may cause future life-threatening refractoriness.

**Antiplatelet Agents**

P2Y₁₂ receptor inhibitors and direct glycoprotein IIb/IIIa inhibitors impair platelet function. Platelets should not be transfused prophylactically without thrombocytopenia, but high-dose therapeutic transfusion may be required for life-threatening hemorrhage in patients on these drugs.⁶⁹ The efficacy of platelet transfusion in cerebral hemorrhage in patients on antiplatelet agents has, however, been questioned.⁷⁰
Massive Transfusion

Massive transfusion is defined as transfusing one complete blood volume or approximately 10 units of red blood cells in the average-sized adult within a 24-hour period. A transfusion target of ≥50,000/μL is recommended for acutely bleeding patients and ≥100,000/μL for those with multiple trauma or CNS injury. The platelet count may fall below 50,000/μL when >1.5–2 blood volumes have been replaced with red cells. In the presence of microvascular bleeding, transfusion may be appropriate when counts are known or suspected to be <100,000/μL. Early aggressive platelet therapy has been associated with improved survival in retrospective studies. The role of algorithms that essentially provide reconstituted whole blood has not yet been determined in prospective randomized controlled studies.

Disseminated Intravascular Coagulation (DIC)

Transfusion is appropriate in children and adults with platelet counts <50,000/μL who have active bleeding, require an invasive procedure, or are otherwise at high risk for bleeding complications.

Pediatrics

Neonates undergoing invasive procedures/surgery or experiencing clinically significant bleeding may be transfused at <50,000/μL.

A prophylactic transfusion trigger of <20,000/μL for stable neonates at term, or <30,000/μL for stable premature neonates, is justified. High-risk neonates (those with
extremely low birth-weight, perinatal asphyxia, sepsis, ventilatory assistance with an FIO₂ >40%, or clinical instability) may be transfused at <30,000/μL at term or at <50,000/μL if premature, due in part to an increased risk of intraventricular hemorrhage.

Infants on extracorporeal membrane oxygenators (ECMO) are usually transfused to maintain a platelet count >80,000–100,000/μL.

**Acute Leukemia and Following High-Dose Chemotherapy**

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

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

Therapeutic transfusion for major bleeding should maintain counts ≥50,000/μL.
Chemotherapy for Solid Tumors

The usual prophylactic transfusion trigger is ≤10,000/μL. The greater risk of bleeding from bladder neoplasms/necrotic tumors and the serious impact of even minor bleeding in patients with limited physiologic reserves may warrant a transfusion trigger of ≤20,000/μL.63

Transfusion Refractoriness73–76

Posttransfusion platelet counts at 10–60 minutes after infusion should be obtained whenever transfusion refractoriness is suspected (successful transfusion defined as a corrected count increment [CCI] ≥7,500/μL per m² per 10¹¹ platelets infused). The 10–60 minute post-infusion count measures transfusion recovery, which is sensitive to immune platelet destruction, splenomegaly, major hemorrhage, or multiple severe non-immune conditions such as sepsis, coagulopathy, graft-versus-host disease, and hepatic veno-occlusive disease. Post-infusion counts at 24 hours assess platelet survival, which is sensitive to non-immune, as well as immune conditions.

Alloimmune refractoriness is more likely in the setting of at least two consecutive poor platelet increments at 10–60 minutes after transfusion. Alloimmunization should be confirmed by demonstration of antibodies to antigens on platelets (that is, human leukocyte antigens [HLA] or human platelet antigens [HPA]). Single donor products identified either by HLA-A and -B locus/HPA matching and/or antibody compatibility, or by crossmatching should be transfused. When these are unavailable, fresh ABO-compatible units are preferred.
The incidence of HLA alloimmunization has been shown to be reduced by the use of leukoreduced cellular blood products in any patient expected to receive multiple platelet transfusions during the course of therapy.

Broadly alloimmunized patients without available matched products do not benefit from unmatched prophylactic platelet transfusions. For active bleeding, these patients may respond to high-dose or continuous platelet transfusion.

**Idiopathic Thrombocytopenic Purpura (ITP)**

Patients who experience major, life-threatening bleeding or intraoperative hemorrhage should receive high-dose platelet transfusions as well as steroids, intravenous immunoglobulin (IVIG) ± other second-line therapies.

Prophylactic transfusions are usually inappropriate since transfused platelets do not survive any longer than patients’ native platelets. Transfusion with IVIG may be considered before minor surgery with platelet counts ≤50,000/μL or major surgery with counts ≤80,000/μL.

**Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS) and Heparin-Induced Thrombocytopenia with Thrombosis (HITT)**

Due to the significant risk of fatal thrombosis, platelets should be transfused only for life-threatening hemorrhage or, possibly, before invasive procedures in patients without thrombotic manifestations.51,52
Posttransfusion Purpura (PTP)
Platelets may be used therapeutically for severe bleeding. Transfusion of randomly selected platelets is usually ineffective. Though efficacy is not well documented, HPA-1a (PI^A1)-negative platelets are frequently given empirically while specific alloantibody testing is in progress. High-dose IVIG is the treatment of choice for PTP.

Neonatal Alloimmune Thrombocytopenia (NAIT)^78
While awaiting response to IVIG, platelet transfusions are indicated for severe thrombocytopenia and/or bleeding. Platelets should lack the HPA recognized by circulating maternal antibodies, although platelets from random donors may be effective when matched platelets are unavailable. If maternal platelets are used, they should be washed or volume-reduced and irradiated. HPA-1a-negative platelets are often used empirically as more than 75% of infants are affected by HPA-1a antibodies.

Aplastic Anemia
Transfuse stable patients prophylactically at counts ≤5,000/μL and patients with fever or minor hemorrhage at counts 6,000–10,000/μL.^79
Components

Approved names: Fresh Frozen Plasma; Plasma Frozen within 24 Hours after Phlebotomy; Plasma Cryoprecipitate Reduced; Plasma Frozen within 24 Hours after Phlebotomy Held at Room Temperature up to 24 Hours after Phlebotomy; Octaplas®, Pooled Plasma (Human), Solvent/Detergent Treated Solution for Intravenous Infusion

Also referred to as FFP, PF24, cryo poor plasma, PF24RT24, and Octaplas®, respectively.

Preparation variations include: Thawed Plasma, Liquid Plasma.

Description of Components

Plasma consists of the noncellular portion of blood that is separated and frozen after donation. It contains coagulation factors, fibrinolytic proteins, immunoglobulins, albumin, and other proteins. Plasma may be prepared from whole blood or collected by apheresis. The anticoagulant solution used and the component volume are indicated on the label. Units prepared from whole blood are approximately 200–250 mL. Apheresis-derived units contain as much as 400–600 mL.

FFP is frozen at -18°C or colder within 6–8 hours of collection (depending upon the anticoagulant), and it
contains physiological quantities of all coagulation factors. PF24 is frozen at -18°C or colder within 24 hours of collection. FFP, PF24, or PF24RT24 can be labeled as Thawed Plasma when stored at 1 to 6°C for a total of five days, including the initial 24-hour post-thaw period. PF24, PF24RT24, and Thawed Plasma contain variably reduced levels of the labile factors V and VIII.\textsuperscript{80,81} Despite these differences, FFP, PF24, PF24RT24, and Thawed Plasma are generally used for the same indications, and are referred to as Plasma in this brochure.

Liquid Plasma is separated no later than five days after the expiration date of the corresponding whole blood unit, and is stored at 1–6°C. Coagulation factor levels in Liquid Plasma are variable and change over time. Liquid Plasma can be used for initial treatment of patients who are undergoing massive transfusion because of life-threatening trauma/hemorrhage and who have clinically significant coagulation deficiencies.

Octaplas\textsuperscript{®} was FDA-approved in the United States in January 2013. It is produced in pools from 630–1,520 donors which undergo 1 μM filtration, solvent-detergent reagent treatment, and affinity column filtration to bind prion protein. Units are supplied in ABO-specific 200 mL volumes.\textsuperscript{82}

Plasma Cryoprecipitate Reduced is produced after thawing, centrifugation, and removal of cryoprecipitate from FFP. It has decreased levels of fibrinogen, Factor VIII and von Willebrand factor, fibronectin, and Factor XIII.\textsuperscript{83} Proteins such as albumin and other coagulation factors
remain at approximately the same levels as in FFP. FFP, PF24, PF24RT24 and Plasma Cryoprecipitate Reduced have equivalent levels of ADAMTS13, the protein that is deficient in thrombotic thrombocytopenic purpura (TTP). ADAMTS13 activity should remain stable for the duration of the shelf life of these thawed products.81

Coagulation factor half-life should be considered when plasma is given prior to invasive procedures. For example, for a patient with a deficiency of Factor VII, the 4–6 hour in vivo half-life of Factor VII mandates transfusion of plasma as close as possible to the time of the procedure to achieve hemostatic factor levels.84

Selection and Preparation

Plasma for transfusion must be ABO-compatible with the recipient’s red cells: for example, group A Plasma is suitable for transfusion to group A and group O patients. Group AB Plasma is suitable for transfusion to patients of all blood types. Frozen plasma must be thawed, usually in a water bath at 30 to 37°C or in an FDA-cleared device, and transfused immediately or stored at 1–6°C for up to 24 hours. Alternatively, once thawed, FFP, PF24 and PF24RT24 may be relabeled as Thawed Plasma and used as a source of stable coagulation factors for up to five days, unless it was collected by apheresis in an open collection system. If collected in a closed system, Plasma Cryoprecipitate Reduced can be used for up to five days post-thaw (and relabeled as Thawed Plasma Cryoprecipitate Reduced).3 Octaplas® has a 12 hour shelf life post-thaw.
Dosing

The dose of plasma is determined by patient size and clinical condition. Plasma should be administered in doses calculated to achieve plasma factor concentrations of at least 30%, which is the minimum hemostatic level for most coagulation factors.\textsuperscript{85–87} This is usually achieved with the administration of 10–20 mL/kg patient weight, though more may be required, depending upon the clinical situation.

When used to correct isolated coagulation factor deficiencies for which no concentrated preparation is available (for example, Factors V or XI), dosing will depend on the pre-transfusion level of the factor, the desired posttransfusion level, the duration of raised levels required, and the factor’s half-life and volume of distribution.\textsuperscript{88}

When used to correct multiple coagulation factor deficiencies, plasma transfusion should be guided by coagulation testing. A prothrombin time (PT) greater than 1.5 times the mid-range of normal, an activated partial thromboplastin time (aPTT) greater than 1.5 times the top of the normal range\textsuperscript{91} or an INR of greater than 1.7.\textsuperscript{89} When such testing is not readily available, clinical evidence of bleeding may be used to direct transfusion decisions.

TTP initially requires the exchange of 1–1.5 plasma volumes daily. In clinical practice, plasma exchange is often tapered as disease activity declines, although this has not been studied prospectively.\textsuperscript{90}
The efficacy of plasma is questionable in many clinical settings, but in general, plasma transfusion is more effective at higher INR values.85

Response

Plasma used to correct coagulation abnormalities should bring the aPTT, PT, and INR within the hemostatic range; but transfusion will not always correct these values, or the correction may be transient.85

Plasma used to treat TTP should result in an increasing platelet count associated with a decrease in serum lactate dehydrogenase.90

Indications and Contraindications1,18,25,55,82,85,87–94

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

- Active bleeding or risk of bleeding due to deficiency of multiple coagulation factors.
- Severe bleeding due to warfarin therapy or urgent reversal of warfarin effect.
- Massive transfusion with coagulopathic bleeding.
- Bleeding or prophylaxis of bleeding for a known single coagulation factor deficiency for which no concentrate is available.
- Thrombotic thrombocytopenic purpura (Plasma or Plasma Cryoprecipitate Reduced).
- Rare specific plasma protein deficiencies for which no concentrate is available.
Octaplas® is indicated for:

- Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease and in patients undergoing cardiac surgery or liver transplant.
- Plasma exchange in patients with thrombotic thrombocytopenic purpura.

Plasma should not be used for the following:

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

*For side effects and hazards, see Appendix 1.*
Liver Disease

Plasma may be used to replace multiple coagulation factor deficiency from liver disease in patients who are actively bleeding or prior to an invasive procedure that would create a risk of bleeding. However, the response may be unpredictable and complete normalization of the hemostatic defect may not occur, therefore posttransfusion coagulation testing may be necessary to evaluate efficacy. Patients with liver disease may safely undergo operative or invasive procedures when the PT is \( \leq 1.5 \) times the mid-range of normal.

Warfarin

Patients on warfarin who experience serious bleeding are treated with Vitamin K (at a dose determined by the INR) and plasma or prothrombin complex concentrates as clinically warranted. Recent guidelines suggest the use of 4-factor prothrombin complex concentrates are preferable to plasma transfusion for situations requiring urgent reversal of warfarin.\(^95\text{–}97\) Three-factor prothrombin complex concentrates with plasma have been proposed as an alternative without supporting randomized controlled trial data. All these suggestions, however, are based on limited evidence from the literature. When prothrombin complex concentrates are not immediately available, plasma transfusion may be necessary. As with liver disease, patients on warfarin may safely undergo operative or invasive procedures when the PT is \( \leq 1.5 \) times the mid-range of normal.
Massive Transfusion and Cardiopulmonary Bypass

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

For massive transfusion, recent trends in the literature based on retrospective studies advocate using a high plasma-to-RBC ratio to improve survival. However, other studies have shown this strategy may increase the risk of multiple organ failure, adult respiratory distress syndrome and other forms of respiratory morbidity. Further studies, including randomized controlled trials, are necessary to determine the risks or benefits of a high-ratio strategy.

Thrombotic Thrombocytopenic Purpura

If plasma exchange is not immediately available, simple transfusion of plasma can be a useful alternative until exchange can be started. With equivalent levels of ADAMTS13, plasma and Plasma Cryoprecipitate Reduced are equally efficacious in the treatment of TTP and newly diagnosed TTP. If ADAMTS13 is used to diagnose and/or monitor the response, a level should be obtained prior to initiation of treatment.
Specific Plasma Protein/Factor Deficiencies

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

- Prophylactic correction of a known factor deficiency for which specific concentrates are unavailable is guided by recommended perioperative hemostatic levels for each type of procedure.
- Treatment or prophylaxis of thromboembolism in antithrombin, protein C, and protein S deficiencies.
- Therapy of acute angioedema or preoperative prophylaxis in hereditary C1-inhibitor deficiency.
- Factor V deficiency (no plasma concentrate available).
- Factor XI deficiency (factor concentrate not available in the U.S.).

Pediatrics

The indications for transfusion of plasma in children are essentially the same as for adults. In infants less than 6 months of age, the levels of vitamin K-dependent coagulants, anticoagulants, and fibrinolytic proteins are decreased, resulting in prolongation of coagulation assays as compared to older children and adults. Despite these differences, hemostatic balance is maintained in the healthy newborn, and spontaneous bleeding or thrombosis are rarely observed. The reserve capacity to respond to pathologic insults in a sick premature infant during the first week of life, however, may be limited.
Components

Approved names: Cryoprecipitated AHF; Pooled Cryoprecipitated AHF.

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

Description of Components

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

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

Cryoprecipitate contains concentrated levels of fibrinogen, Factor VIII:C, Factor VIII:vWF (von Willebrand factor), Factor XIII, and fibronectin. Each unit of cryoprecipitate should contain a minimum of 80 IU of Factor VIII:C and 150 mg of fibrinogen in 5–20 mL of plasma. Mean American Red Cross single/pool-of-five content for blood group O: Factor VIII:C 140/680 IU and fibrinogen 410/2100 mg/dL, respectively. Cryoprecipitate from other ABO blood group plasma contains ~30% higher levels of Factor VIII:C.
Selection and Preparation

Cryoprecipitate is considered to be an acellular blood component. Compatibility testing is unnecessary, though cryoprecipitate that is ABO-compatible with recipient red cells is preferred. Rh type need not be considered.

CMV testing and leukoreduction are not required. Frozen cryoprecipitate is thawed in a protective plastic overwrap in a waterbath at 30–37°C up to 15 minutes or in an approved microwave. Thawed cryoprecipitate should be kept at room temperature and transfused as soon as possible. If it is from a closed single unit or has been pooled using an FDA-approved sterile connecting device, it should be transfused within 6 hours of thawing. If it is an open system or if pooling of the thawed cryoprecipitate requires the unit containers to be entered in an open fashion, units should be transfused within 4 hours.

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

Dosing and Response

For hypo/dysfibrinogenemia, cryoprecipitate units required can be estimated by the following:

1. Weight (kg) × Blood Volume/kg* (mL/kg) = Blood Volume (mL)
2. Blood Volume (mL) × (1.0-Hematocrit) = Plasma Volume (mL)
3. Fibrinogen required (mg) = (desired fibrinogen level [mg/dL] – initial fibrinogen level [mg/dL]) × Plasma Volume [mL] × 0.01 [dL/mL] ÷ 0.6†

* Mean estimate of Blood Volume/kg ≈ 65 mL/kg, average adult female; 70 mL/kg, average adult male; 80–105 mL/kg, preterm neonate; 90 mL/kg, term neonate; 85 mL/kg, 1–6 months, 75 mL/kg, 6 months–12 years.¹¹³,¹¹⁴

† Average percent fibrinogen recovery¹¹⁵

For example, to increase fibrinogen from 50 to 100 mg/dL in an adult female (65 kg, 40% hematocrit):
1. 65 kg × 65 mL/kg = 4,225 mL blood volume
2. 4,225 mL × (1.0–0.4) = 2,535 mL plasma volume
3. Fibrinogen required = (100 mg/dL–50 mg/dL) × 2,535 mL × 0.01 dL/mL ÷ 0.6 = 2,112 mg
(Thus, 2,112 mg ÷ 2100 mg average ARC pool content ≈ 1 pool or 2,112 mg ÷ 410 mg average ARC unit content ≈ 5 units)

Pre-transfusion and posttransfusion fibrinogen levels should be determined to assess the adequacy of the cryoprecipitate dose. The frequency of dosing depends on the rate of consumption, degree of fibrinogen recovery and half-life (check serial levels). That half-life is approximately 4 days in the absence of increased consumption (for example, bleeding, disseminated intravascular coagulation).
Indications and Contraindications

Cryoprecipitate is indicated for bleeding associated with fibrinogen deficiencies. Alternative uses in congenital fibrinogen deficiency, dysfibrinogenemia, Factor XIII deficiency, hemophilia A, or von Willebrand disease are not recommended and should be considered only when the specific factor concentrate is not available. Use of this component may be considered for uremic bleeding after other modalities have failed. For side effects and hazards, see Appendix 1.
Acquired Fibrinogen Deficiency and Bleeding

Cardiac surgery is the most common surgical circumstance for cryoprecipitate transfusion. Excessive bleeding associated with worsened morbidity and mortality may result from coagulopathy due to exposure of the blood to artificial surfaces, hemodilution, hypothermia, and/or acidosis.\(^{117}\) Established general guidelines have recommended maintaining fibrinogen levels above 100 mg/dL in bleeding patients\(^{118}\), although this number was not based on clinical trials and more recent studies in obstetric, trauma, and cardiac surgery patients indicate higher levels (150–200 mg/dL)\(^ {119–121}\) improve in vitro parameters and may improve clinical outcomes. Further clinical validation, including use of cryoprepitate as the fibrinogen source, is required.

Fibrin Sealant

Commercially produced, virus-inactivated fibrin sealant is preferable to cryoprecipitate with respect to safety and efficacy.

Massive Transfusion

Transfusion for bleeding is often required after one or more blood volumes have been replaced when fibrinogen levels may decrease to <100 mg/dL.\(^ {122}\) Algorithms employing early fibrinogen infusion have not been validated for efficacy or
for safety with cryoprecipitate, but higher levels (150–200 mg/dL) may be beneficial in treating trauma, obstetric, and cardiac surgery patients.\textsuperscript{103,117,119–124}

**Uremic Bleeding**

Other modalities such as 1-deamino-8-D-arginine vasopressin (DDAVP) are preferred. Cryoprecipitate is used in the failure or absence of other treatments, though effectiveness has not been uniformly observed.\textsuperscript{8,123}

**Disseminated Intravascular Coagulation (DIC)**

Although transfusion in DIC is not based on lab values, severe hypofibrinogenemia (<100–150 mg/dL) that persists despite FFP replacement may be treated with cryoprecipitate.\textsuperscript{104}

**Congenital Factor Deficiencies**

**Congenital Fibrinogen Deficiency**

In 2009, a human-derived, virus-inactivated fibrinogen concentrate was FDA approved and is now considered first-line treatment for congenital fibrinogen deficiency.\textsuperscript{116,124}

For spontaneous bleeding, prior to surgery, or to prevent fetal loss throughout pregnancy, recommendations are to keep fibrinogen levels above 100 mg/dL. After surgical or spontaneous bleeding is stopped, levels above 50 mg/dL should be maintained until wound healing is complete.\textsuperscript{104}
**Hemophilia A and von Willebrand Disease (vWD)**

Cryoprecipitate is not recommended unless recombinant or virus-inactivated Factor VIII:C or Factor VIII:vWF concentrates are not available. DDAVP is the treatment of choice for type 1 vWD.\textsuperscript{121}

**Factor XIII Deficiency**

Deficiency of Factor XIII presents risk for severe bleeding, spontaneous abortion, and spontaneous intracranial hemorrhage (25–40%). Cryoprecipitate is not recommended and only used if virus-inactivated Factor XIII concentrates are not available.\textsuperscript{116}

Due to the high incidence of intracranial hemorrhage, newborns and some adults receive prophylactic dosing.
Blood Component Modifications

1. Leukocyte-Reduced Components

Description and Preparation of Components

Alternative terminology: leukocyte reduction, leukoreduction, leukoreduced, LR, leukocyte-poor, leuko-poor.

Leukoreduction is a process by which white blood cells are removed from the blood component. This may be accomplished in-process during apheresis collection or by filtration of the blood product, either in the manufacturer’s laboratory (pre-storage), or at the patient’s bed-side (post-storage). Of the latter, prestorage leukocyte reduction is preferable as it is more readily subjected to rigorous quality control and removes leukocytes prior to the release of cytokines, cellular debris, and intracellular microorganisms. This may also reduce erythrocyte storage-induced damage and transfusion reactions, and decrease the risk of infection.

Blood products customarily leukoreduced: red blood cells (RBCs), apheresis platelets, whole blood-derived (WBD) platelets.

The average whole blood unit contains $\geq 1 \times 10^9$ leukocytes at collection. To meet quality standards, a leukoreduced component, whether it be a unit of RBCs, apheresis platelets, or prestorage-pooled WBD platelets, must have a
final white blood cell count of \(<5 \times 10^6\). In order for pooled WBD platelets to achieve this criterion, each single WBD platelet unit must have a residual leukocyte count of \(<8.3 \times 10^5\) per unit.\(^3\)

**Indications** 126–129,132,133

- To reduce the incidence of recurrent febrile non-hemolytic transfusion reaction (FNHTR) by as much as 60%.
- To reduce HLA alloimmunization and HLA-mediated platelet refractoriness by 50–80%.
- To reduce transfusion transmission of intracellular pathogens such as cytomegalovirus (see Blood Component Modifications, Section 2) and Human T-Lymphotropic Virus (HTLV)- I/II. Reduction of viral load has been demonstrated for EBV, without published clinical effectiveness data.

**Additional Comments**

- Apheresis Granulocytes is, by definition, a blood product transfused for its white blood cell content and thus must not be leukoreduced.
- Leukoreduction does not eliminate the presence of all white blood cells. This persistence of residual donor leukocytes may result in microchimerism, which can lead to transfusion-associated graft-versus-host disease (TA-GVHD). For such at-risk patients (refer to section: Irradiated Components), cellular products must be irradiated.\(^{130}\)
2. Cytomegalovirus (CMV)-Reduced-Risk Components

Description and Preparation of Components

CMV is an intracellular virus transmissible by cellular blood components which may have detrimental effects in immunocompromised patients. Of potential U.S. donors over age 17, 50–90% have been exposed to CMV. Blood products that are considered to carry reduced risk, include the following:

- CMV-seronegative cellular blood components: collected from individuals who have tested negative by an FDA-approved screening test for CMV antibodies. Residual risk remains as donors may have been tested within the “window period” of 6–8 weeks, the time before CMV antibodies develop after initial exposure. Alternately, over time, donors’ antibody titers may decrease to undetectable levels, resulting in false-negative serostatus.

- Leukoreduced cellular blood components: Residual risk may remain due to the presence of cell-free virus and/or residual infected WBCs found in the product.

Additional Comments

- Frozen/deglycerolized RBCs, transfused before the availability of modern leukoreduction filters, do not dependably contain equivalent residual leukocyte counts to leukoreduced RBCs. Plasma products have not been reported to transmit CMV.

- CMV-reduced-risk components are not considered necessary for patients receiving chemotherapy unless they are severely immunosuppressed.
• For recipients requiring CMV-reduced-risk granulocyte transfusions, the donor should be CMV-seronegative since these products cannot undergo leukoreduction.

• The CMV serostatus of chronically transfused infants should be checked monthly if initially seronegative.

• Final determination of product choice may be dependent on product availability and patient need with the understanding of associated risk.¹³⁷

3. Irradiated Components

Description and Preparation of Components

A severe and potentially fatal consequence of transfused leukocytes is transfusion-associated graft-versus-host disease (TA-GVHD), a reaction that occurs in a recipient incapable of mounting an immune response against the foreign donor-derived white blood cells. A disparity of HLA antigen types results in the donor mounting a cellular immune response that damages the host tissue.¹⁴²

Inactivating donor lymphocytes by gamma- or X-irradiation can prevent the proliferation of these transfused cells and the development of TA-GVHD. AABB-recommended irradiation exposure dosages consist of the following: central portion of the container, 25–50 Gy (2,500–5,000 cGy); with the remainder of the irradiation container ≥15 Gy.²,³

All cellular products given to immune-suppressed patients (RBCs, apheresis granulocytes, whole blood-derived platelets, apheresis platelets) require irradiation as does any plasma product that has never been frozen. TA-GVHD has not been reported in association with use of cryoprecipitate
or frozen plasma, thus these components do not require irradiation.\textsuperscript{149}

The expiration date of irradiated RBCs is decreased to the original expiration date or 28 days post-irradiation, whichever occurs sooner. Irradiation has no deleterious effect on platelets, and the expiration date remains unchanged.\textsuperscript{3}

For those patients who are sensitive to the elevated extracellular levels of potassium that can accumulate during storage of post-irradiated RBC units, removal of the residual plasma by washing is recommended.\textsuperscript{143}

**Indications**\textsuperscript{144,145}

- Intrauterine transfusion and infants who have received IUTs
- Pediatric patients: infants and children with or suspected to have an immune deficiency
- Congenital cellular immunodeficiency (for example, severe combined immunodeficiency—SCID, Di-George syndrome)
- Hodgkin disease
- Granulocyte transfusions
- Blood product from a related donor (any degree relation), regardless of the patient’s immune status
- Blood product from an HLA-selected or crossmatched donor, regardless of patient’s immune status
- Hematopoietic progenitor cell (HPC) transplant recipients (allogeneic, autologous)
- Patient receiving T-cell suppression therapy: purine nucleoside analogs (for example, fludarabine, bendamustine, azathioprine), alemtuzumab
4. Washed Cellular Components

Description and Preparation of Components

Using an automated device, a cellular blood product (that is, RBCs or platelets) is repeatedly washed with normal saline solution (0.9% Sodium Chloride Injection, USP). In this manner, there is a >95% reduction of plasma and its constituents.\textsuperscript{148}

With this process, the anticoagulant-preservative solution and plasma are removed, with a concomitant reduction of the washed unit’s expiration date: RBCs to 24 hours (open system) and platelets (whole blood-derived or apheresis) to 4 hours. The product’s overall recovery yield, dependent on type of automated blood cell processor used and age of component, can result in an approximate cellular loss of 20% for a RBC unit and 33% or more for platelet units.\textsuperscript{3,148}

Indications\textsuperscript{146,147,149}

- Anaphylactic and recurrent significant allergic transfusion reactions unresponsive to pre-medication.
- For recipients with IgA deficiency, particularly those with a prior anaphylactic reaction, platelet washing is an alternative when the need is urgent and a product from an IgA-deficient donor cannot be located. IgA-deficient donor RBCs are less-commonly used due to their unavailability and the relative ease of RBC washing or obtaining frozen/deglycerolized RBCs.
- Avoidance of hyperkalemia in patients predisposed to arrhythmia from rapid transfusion and/or large volumes (for example, neonates, patients with superior vena caval/atrial lines, or renal disease).
- Neonatal Alloimmune Thrombocytopenia (NAIT): severe congenital thrombocytopenia due to maternal anti-platelet antibody directed against a paternally derived fetal platelet antigen (for example, HPA-1a). Washing of maternal platelets will remove the antibody.
- Recurrent febrile non-hemolytic transfusion reactions (FNHTRs) in patients unresponsive to leukocyte-reduced products and anti-pyretic pre-treatment.

**Additional Comments**

- Leukoreduction remains the preferred means of reducing alloimmunization, CMV transmission, and FNHTRs.
- Bacterial contamination remains a risk when using an open system.
- The risk of transfusion transmission of infectious organisms such as HIV and viral hepatitis is unaffected in washed blood products.
- The risk for transfusion-associated graft-versus-host disease (TA-GVHD) is also unaffected in washed blood products.
- An alternative to washing RBC units when potassium is an issue is the use of fresher (<5-day-old) products.
- As volume reduction does not adequately reduce the supernatant plasma proteins in platelet units, washing is preferred for the prevention of allergic transfusion reactions and preparation of units for NAIT recipients.148
The Hospital Transfusion Committee

Overview

In an effort to ensure the safety and efficacy of transfusions, several regulatory and accrediting agencies—including the Joint Commission, the AABB, CMS and the College of American Pathologists—require hospitals to monitor blood transfusion practices and adverse events. Further, both the Joint Commission and the Code of Federal Regulations (CFR) require a hospital to develop, implement and maintain an effective, ongoing, hospital-wide, data-driven, quality-assessment and performance-improvement program, which includes transfusion services. These agencies do not mandate how the hospital should accomplish these tasks, only that they be performed. For this reason, the approach in monitoring transfusion practices may vary: either a multidisciplinary Transfusion Committee (TC) may be developed or the task may fall under the purview of other departmental specialties, such as quality assurance, surgery or critical care services. As medical centers consolidate, a current trend in Canada is to establish regional TCs. The benefits of regional TCs include taking advantage of expertise from multiple sites and facilitating the development of standard processes across a region to improve consistency in practice. The TC is an important facet of the overall blood management program at an institution.2,3,151–156
Membership

A multidisciplinary approach allows for better quality assessment and performance improvement. The TC should include representatives from the medical staff (such as those from surgery, anesthesia, medicine, hematology, and pediatrics), nursing, quality services, and the transfusion service. The inclusion of blood product providers should be considered an asset. The medical director of the transfusion service is a vital contributor to the committee and may or may not serve as chair. The chair should, however, be a physician knowledgeable in transfusion medicine.

Functions

The responsible TC should address, through review or audit, the following aspects of transfusion, as incorporated in policies and procedures (list may not be all inclusive):

- Ability of transfusion services to meet patient needs
- Appropriate utilization
- Blood administration policies
- Blood ordering and refusal practices
- Blood distribution, handling, and dispensing
- Clinical alternatives to blood transfusion (for example, erythropoietin, perioperative salvage)
- Compliance with peer-review recommendations
- Evaluation of evolving technologies and products
- Infectious and non-infectious adverse events
- Informed consent
- Medical errors, near misses, and sentinel events
• Monitoring of patients for appropriate responses
• Patient identification
• Performance improvement measures
• Pretransfusion testing orders
• Sample collection and labeling
• Training staff involved in transfusion
• Wastage and discard rates\textsuperscript{2,154,155}

**Process**

A key function of the committee is to establish transfusion guidelines for the administration of each blood component transfused at the institution, using current peer-reviewed medical literature as a resource. The guidelines should be approved by the medical staff prior to implementation. TC members should meet regularly to review various aspects of blood transfusion and provide revision, as necessary.

The aim for developing transfusion guidelines is to remind ordering physicians of practices for which there is general support and clinical trial evidence. These guidelines provide an overview of selected subject matter with reference to alternative literature resources, but they cannot be expected to cover every instance in which a transfusion is indicated. In every case, however, the rationale for transfusion should be clearly documented in the medical record. Guidelines should be available electronically for ease of access.\textsuperscript{157}

The review of transfusions can be done prospectively, prior to issuing blood units, by the transfusion service personnel or retrospectively by the transfusion service and TC. For most transfusions, where large numbers of blood products
are utilized, a retrospective review is adequate and more commonly used. These reviews are best conducted immediately after the transfusion event instead of months later. For certain high-cost blood products, prospective review may be appropriate to prevent unnecessary transfusions. Similarly, potentially inappropriate orders—for example, a request for platelet transfusion to a patient with thrombotic thrombocytopenic purpura or an order for four units of red blood cells for a small child—may also require review prior to blood issue. To assist in the performance of such a review, several medical centers have created a staff position known as the Transfusion Coordinator or Transfusion Safety Officer; this individual is responsible for performing audits, hemovigilance monitoring, and staff education and acts as a liaison among the various departments.157

Another form of review is the transfusion quality audit. As an example, trained hospital quality assurance or compliance staff may perform chart or electronic record reviews, using the approved transfusion guidelines developed by the TC. When there are questions about the indications and results of a transfusion, the clinical records should be brought to the attention of the TC, and the TC should follow its policies for further action as needed.

Some hospitals have successfully implemented concurrent electronic screening of blood orders. Also known as clinical decision support systems (CDSSs), these alerts can be created within computerized physician order entry (CPOE) interfaces to provide evidence-based guidance on the appropriate use of blood products at the moment of ordering. CDSSs have been shown to be effective in
improving patient management and their efficacy was enhanced when implemented after a focused educational campaign on blood product utilization.\textsuperscript{158}

**Monitors**

Various quality indicators should be monitored and tracked. Performance-improvement measures should be put in place where indicated. Finally, the TC should have a mechanism in place to periodically assess its own effectiveness. Examples of indicators that may be tracked include, but are not limited to the following:

- Adverse reactions to administered blood products
- Biological product deviations or patient transfusion-related fatalities, reportable to the Food and Drug Administration
- Blood usage parameters as established by the institution, clinical department, physician, diagnosis (Diagnosis-Related Groups), or surgical procedure
- Crossmatch-to-transfusion ratio
- Near-miss events defined as deviations from established procedures and recognized before being carried out
- Patient monitoring during transfusion
- Sample collection and labeling, including "wrong blood in tube"
- Sentinel reports to the Joint Commission
- Suspected transfusion-transmitted infections
- Turnaround times for emergency requests
- Wastage of all blood components, both allogeneic and autologous\textsuperscript{253,159,160}
Reports

A TC member should be designated as secretary to document activities, distribute minutes and reports of the group’s work for submission to other entities of the hospital (for example, clinical departments of the medical staff, the Medical Staff Executive Committee, the Clinical Practices Committee, and the Credentials Committee). The intent of these documents is to provide other peer-review committees with a record of the actions taken to ensure appropriate transfusion-related patient care. These minutes may be protected from inappropriate legal discovery as a critical component of an institution’s quality-monitoring program.160
Appendix 1: Side Effects and Hazards of Blood Transfusion

The following sections are reproduced from the April 2013 Circular of Information (COI) for blood and blood components. References to sections in this appendix refer to COI sections.

Side Effects and Hazards for Whole Blood and All Blood Components

Immunologic Complications, Immediate

1. Hemolytic transfusion reaction, the destruction of red cells, is discussed in detail in the section on components containing red cells and in the platelet section.

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

3. Febrile nonhemolytic reaction is typically manifested by a temperature elevation of > 1°C or 2°F occurring during or shortly after a transfusion and in the absence of any other pyrexic stimulus. This may reflect the action of antibodies against white cells or the action of cytokines either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may occur in less than 1% of transfusions of leukocyte-reduced red cell components and about 5% of leukocyte-reduced apheresis platelet components. Febrile reactions occur more frequently in patients receiving non-leukocyte-reduced components and those previously alloimmunized
by transfusion or pregnancy. No routinely available pre- or posttransfusion tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief. Patients who experience repeated, severe febrile reactions may benefit from receiving leukocyte-reduced components. If these reactions are caused by cytokines in the component, prestorage leukocyte reduction may be beneficial.

4. **Allergic reactions** frequently occur (i.e., 1–3% of plasma-containing components) as mild or self-limiting urticaria or wheezing that usually respond to antihistamines. More severe manifestations, including respiratory and cardiovascular symptoms, are more consistent with anaphylactoid/anaphylactic reactions and may require more aggressive therapy (see below). No laboratory procedures are available to predict these reactions.

5. **Anaphylactoid/anaphylactic reactions**, characterized by hypotension, tachycardia, nausea, vomiting and/or diarrhea, abdominal pain, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm, are rare but dangerous complications requiring immediate treatment with epinephrine. These reactions have been reported in IgA-deficient patients who develop antibodies to IgA antibodies. 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. Similar reactions have also been described in patients with haptoglobin deficiency. In certain circumstances, patients may benefit from the use of washed cellular components to prevent or reduce the severity of allergic reactions not minimized by treatment with medication alone.
Transfusion-related acute lung injury (TRALI) is characterized by the acute onset of hypoxemia and noncardiogenic pulmonary edema within 6 hours of a blood or blood component transfusion in the absence of other causes of acute lung injury or circulatory overload. Various stimuli in blood components, most commonly white blood cell (WBC) antibodies from donors sensitized during pregnancy or prior transfusion or transplantation, or proinflammatory molecules that accumulate in stored blood components, may cause TRALI. These mechanisms may not be mutually exclusive and may act synergistically with underlying patient factors to lead to a final common pathway of acute lung injury. These stimuli may trigger an inflammatory response, granulocyte activation and degranulation, and injury to the alveolar capillary membrane, and the development of permeability pulmonary edema. Although most TRALI cases are associated with donor antileukocyte antibodies, rare cases have implicated recipient antileukocyte antibodies that reacted with donor leukocytes. Widespread leukoreduction of blood components has likely mitigated this latter risk. Laboratory testing of blood donors for antileukocyte antibodies or blood components for biologic mediators does not alter management of this reaction, which is diagnosed on clinical and radiographic findings. Treatment of TRALI involves aggressive respiratory support, and often mechanical ventilation. The preferential use of plasma collected from male donors has been associated with a significant reduction in the number of reported TRALI cases and associated fatalities. Transfusion services should immediately report suspected TRALI to the blood-collection facility to facilitate the retrieval of other components associated with the involved donation(s) or prior donations.
Immunologic Complications, Delayed

1. Delayed hemolytic reaction is described in detail in the [COI section] on components containing red cells.

2. Alloimmunization to antigens of red cells, white cells, platelets, or plasma proteins may occur unpredictably after transfusion. Blood components may contain certain immunizing substances other than those indicated on the label. For example, platelet components may also contain red cells and white cells. 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 be detected only by specialized testing.

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

4. Transfusion-associated graft-vs-host disease (TA-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 recipient tissue antigens. TA-GVHD can occur if the host does not recognize and reject the foreign transfused cells, and it can follow transfusion of any component that contains even very small numbers of viable T lymphocytes. Recipients with severe cellular immunodeficiency (except for HIV infection) are at greatest risk (e.g., fetuses receiving intrauterine transfusions, recipients of hematopoietic progenitor cell transplants, and selected patients with severe immunodeficiency conditions), but TA-GVHD has also been reported in recipients receiving purine analogues (e.g., fludarabine, cladribine) for oncologic and rheumatologic diseases, and in immunologically normal recipients who are heterozygous for a tissue antigen haplotype for which the donor is homozygous. Tissue antigen haplotype sharing is most likely to occur when the transfused component is from a blood relative or has been selected for HLA compatibility. TA-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 TA-GVHD.

Nonimmunologic Complications

1. Because Whole Blood and blood components are made from human blood, they may carry a risk of transmitting infectious agents [e.g., viruses, bacteria, parasites, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the CJD agent]. Careful donor selection and available laboratory tests do not totally eliminate these hazards. Also, septic and toxic reactions can result from transfusion of bacterially contaminated blood and blood
components. Such complications are infrequent, but may be life-threatening. Infectious disease transmission 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 Testing of Donor Blood [CO1 section]). These procedures do not totally eliminate the risk of transmitting these agents. Transfusion services should immediately report infections that may be related to the blood donor or to the manufacture of the blood components to the collection facility.

2. *Cytomegalovirus* (CMV) may be present in white-cell containing components from donors previously infected with this virus, which can persist for a lifetime despite the presence of serum antibodies. Up to 70% of donors may be CMV seropositive. Transmission of CMV by transfusion may be of concern in low birth-weight (≤1200 g) premature infants born to CMV-seronegative mothers and in intrauterine transfusions and/or certain other categories of immunocompromised individuals such as hematopoietic progenitor cell or solid organ transplant patients, 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 (e.g. *Babesia* spp, *Leishmania* spp, and *Plasmodia* spp) there are no routinely available tests to predict or prevent disease transmission. All potential blood donors are subjected to screening procedures intended to reduce to a minimum the risk that they will transmit infectious agents.
3. *Bacterial sepsis* occurs rarely but can cause acute, severe, sometimes life-threatening effects. Onset of high fever (≤2°C or ≤3.5°F increase in temperature), severe chills, hypotension, or circulatory collapse during or shortly after transfusion should suggest the possibility of bacterial contamination and/or endotoxin reaction in the transfused products. Although platelet components stored at room temperature have been implicated most frequently, previously frozen components thawed by immersion in a waterbath and red cell components stored for several weeks at 1°C to 6°C have also been implicated. Although most platelet components are routinely tested for bacterial contamination, this does not completely eliminate the risk. Both gram-positive and gram-negative organisms have been identified as causing septic reactions. Organisms capable of multiplying at low temperatures (e.g., *Yersinia enterocolitica*) and those using citrate as a nutrient are most often associated with components containing red cells. A variety of pathogens, as well as skin contaminants, have been found in platelet components. Endotoxemia in recipients has resulted from multiplication of gram-negative bacteria in blood 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, 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. It is important to report all febrile transfusion reactions to the transfusion
service for appropriate investigation. If posttransfusion sepsis is suspected, the transfusion service should immediately report the reaction to the blood collection facility to facilitate retrieval of other potentially contaminated components associated with the collection.

4. *Transfusion-associated circulatory overload* (TACO) leading to cardiogenic (hydrostatic) pulmonary edema can occur after transfusion of excessive volumes or at excessively rapid rates. This is a particular risk in individuals with underlying cardiopulmonary or renal disease, the very young and 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 supernatant fluid in cellular components, reduced to a minimum.

5. *Hypothermia* carries a risk of cardiac arrhythmia or cardiac arrest and exacerbation of coagulopathy. Rapid infusion of large volumes of cold blood or blood components 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 or blood components is needed. Warming must be accomplished using an FDA-cleared blood-warming device so as not to cause hemolysis.
6. *Metabolic complications* may accompany large-volume transfusions, especially in neonates and patients with liver or kidney disease.

a) Citrate “toxicity” reflects a depression of ionized calcium caused by 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 or blood components 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 electrocardiogram 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 preexisting 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 blood component transfusion, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), should be notified as soon as possible (telephone: 301-827-6220; email: fatalities2@fda.hhs.gov). Within 7 days after the fatality, a written report must be submitted to the FDA/CBER, Director, Office of Compliance and Biologics Quality, Attn: Fatality Program Manager, 1401 Rockville Pike, Suite 200N, 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/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/default.htm.
Appendix 2: Published Estimates of Transfusion Risks

The incidence of adverse reactions after transfusion varies widely among studies because published estimates depend on a number of factors, including but not limited to the patient population (e.g., underlying disease, concurrent medication, immunosuppression), component type and preparation method, case definitions and surveillance activities for reporting transfusion reactions. Therefore, it is important to consider the many factors that affect the estimates of incidence in different clinical settings.

In the Table on the next page, the incidence is expressed as a percentage if greater than 0.1% or a ratio if less than 0.1%. The denominator is the number of transfusions, unless otherwise noted as the number of distributed components. A range is given, if possible, and the reader is referred to the citations for additional information.
## Transfusion Reactions, Immediate

<table>
<thead>
<tr>
<th>Description</th>
<th>Estimated incidence</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hemolytic transfusion reaction (incompatible red cells)</td>
<td>1 per 12,000–38,000&lt;br&gt;Fatal: 1 per 600,000–1.5 million</td>
<td>About 2–7% of ABO-mistransfusion events are fatal</td>
<td>161–164</td>
</tr>
<tr>
<td>Acute hemolytic transfusion reactions (incompatible plasma)</td>
<td>1 per 46,000</td>
<td>About 21% of platelet transfusions were incompatible in the retrospective cohort study</td>
<td>165</td>
</tr>
<tr>
<td>Immune-mediated platelet destruction (refractoriness to platelet transfusion)</td>
<td>4–13%</td>
<td>About 50% of HLA-alloimmunized patients become refractory to prestorage leukoreduced components</td>
<td>112, 165</td>
</tr>
<tr>
<td>Febrile nonhemolytic reaction</td>
<td>RBC: 0.1–0.4%&lt;br&gt;Platelet concentrates: 0.1%&lt;br&gt;Apheresis platelets: 4–8%</td>
<td>Prestorage leukoreduced cellular components</td>
<td>161, 162, 133, 166, 167</td>
</tr>
<tr>
<td>Allergic reaction (mild)</td>
<td>RBC: 0.1–0.6%&lt;br&gt;Apheresis platelets: ~5%&lt;br&gt;Plasma: 1–3%</td>
<td>Prestorage leukoreduced cellular components</td>
<td>161, 162, 168</td>
</tr>
<tr>
<td>Anaphylactoid/anaphylactic reactions</td>
<td>1 per 20,000–50,000</td>
<td></td>
<td>161, 162, 168</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury (TRALI)</td>
<td>1 per 12,000 transfusions&lt;br&gt;ARC surveillance (per distributions), 2013&lt;br&gt;RBC: 1 per 480,000&lt;br&gt;Plasma: 1 per 240,000&lt;br&gt;Apheresis platelets: 1 per 138,000</td>
<td>Plasma collected predominantly from male donors</td>
<td>169, 170</td>
</tr>
<tr>
<td>Description</td>
<td>Estimated incidence</td>
<td>Comment</td>
<td>References</td>
</tr>
<tr>
<td>-----------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Transfusion-associated circulatory overload (TACO)</td>
<td>1–8%</td>
<td></td>
<td>161-163</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>No published estimates—more likely to occur with massive transfusion or in pediatric and neonatal patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic complications (hypocalcemia, acidosis/alkalosis; hyper- or hypokalemia)</td>
<td>No published estimates—more likely to occur with massive transfusion or in pediatric and neonatal patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic transfusion reaction</td>
<td>See Appendix 5A, Bacteria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Transfusion Reactions, Delayed

<table>
<thead>
<tr>
<th>Description</th>
<th>Estimated Incidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed hemolytic transfusion reaction</td>
<td>1 per 5,400–62,000</td>
<td>161, 162, 171</td>
</tr>
<tr>
<td></td>
<td>Fatal: 1 per 1.8 million</td>
<td></td>
</tr>
<tr>
<td>Alloimmunization (red cell antigens) [Delayed serologic transfusion reaction]</td>
<td>1 per 1,500–3,000 0.5% per RBC transfused</td>
<td>161, 162, 171, 172</td>
</tr>
<tr>
<td>Alloimmunization [human leukocyte antigens (HLA), human platelet antigens (HPA)] (prestorage leukoreduced components)</td>
<td>HLA: 10–17% of multiply-transfused patients  HPA: 2–10% of multiply-transfused patients</td>
<td>127</td>
</tr>
<tr>
<td>Posttransfusion purpura (PTP)</td>
<td>Less than 1 in 2,000,000</td>
<td>161, 162</td>
</tr>
<tr>
<td>Transfusion-associated graft-vs-host disease (TA-GVHD)</td>
<td>Exceedingly rare; case reports with nonirradiated cellular components</td>
<td>161, 162</td>
</tr>
</tbody>
</table>
## Appendix 3: Brief History of Infectious Disease Testing in the United States

<table>
<thead>
<tr>
<th>Disease or Infection</th>
<th>Analyte</th>
<th>Year Introduced (modified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td><em>Treponema pallidum</em></td>
<td>1950s</td>
</tr>
<tr>
<td></td>
<td>antibodies</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B surface antigen (HBsAg)</td>
<td>1971</td>
</tr>
<tr>
<td></td>
<td>Anti-HBc</td>
<td>1986</td>
</tr>
<tr>
<td></td>
<td>DNA</td>
<td>2008–2009</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Anti-HCV</td>
<td>1990; 1992; 1997</td>
</tr>
<tr>
<td></td>
<td>RNA</td>
<td>1999</td>
</tr>
<tr>
<td>AIDS; HIV</td>
<td>Anti-HIV-1/2</td>
<td>1985; 1992; 2009</td>
</tr>
<tr>
<td></td>
<td>RNA</td>
<td>1999</td>
</tr>
<tr>
<td>HTLV</td>
<td>Anti-HTLV-I/II</td>
<td>1988; 1998</td>
</tr>
<tr>
<td>WNV</td>
<td>RNA</td>
<td>2003</td>
</tr>
<tr>
<td>Chagas</td>
<td><em>Trypanosoma cruzi</em></td>
<td>2007 (universal)</td>
</tr>
<tr>
<td></td>
<td>(<em>T. cruzi</em>) antibodies</td>
<td>2009 (selective, donor-based testing)</td>
</tr>
</tbody>
</table>

Abbreviations: AIDS, acquired immuno deficiency syndrome; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; WNV, West Nile virus.
### Appendix 4: Routine American Red Cross Infectious Disease Test Methods (2013)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Marker</th>
<th>Assay method</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>HBsAg (screen)</td>
<td>Chemiluminescent immunoassay (ChLIA)</td>
<td>Abbott PRISM</td>
</tr>
<tr>
<td></td>
<td>HBsAg (confirmatory)</td>
<td>ChLIA, neutralization</td>
<td>Abbott PRISM</td>
</tr>
<tr>
<td></td>
<td>Anti-HBc (screen)^</td>
<td>ChLIA</td>
<td>Abbott PRISM</td>
</tr>
<tr>
<td></td>
<td>HBV DNA (screen)*</td>
<td>Nucleic acid test (transcription mediated amplification; TMA)</td>
<td>Novartis PROCLEIX Ultrio Plus (HIV-1/ HCV/ HBV)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Anti-HCV (screen)</td>
<td>ChLIA</td>
<td>Abbott PRISM</td>
</tr>
<tr>
<td></td>
<td>Anti-HCV (confirmatory)</td>
<td>Enzyme-linked immunoassay (EIA)</td>
<td>Ortho-Clinical Diagnostics HCV ELISA version 3.0 (outsourced)</td>
</tr>
<tr>
<td></td>
<td>HCV RNA (screen)*</td>
<td>TMA</td>
<td>Novartis PROCLEIX Ultrio Plus (HIV-1 /HCV/ HBV)</td>
</tr>
<tr>
<td>HIV-1, -2</td>
<td>Anti-HIV-1/HIV-2 (HIV O Plus) (screen)</td>
<td>ChLIA</td>
<td>Abbott PRISM</td>
</tr>
<tr>
<td></td>
<td>Anti-HIV-1/HIV-2 (confirmatory and differentiation)</td>
<td>HIV-1 indirect immunofluorescence assay (IFA); HIV-2 EIA; Multispot HIV-1 / HIV-2 rapid test</td>
<td>Sanochemia IFA; Bio-Rad EIA and rapid test</td>
</tr>
<tr>
<td></td>
<td>HIV RNA (screen)*</td>
<td>TMA</td>
<td>Novartis PROCLEIX Ultrio Plus Assay (HIV-1/ HCV/ HBV)</td>
</tr>
<tr>
<td>Disease</td>
<td>Marker</td>
<td>Assay method</td>
<td>Trade name</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>HTLV I/II</td>
<td>Anti-HTLV-I/HTLV-II (screen)</td>
<td>ChLIA</td>
<td>Abbott PRISM</td>
</tr>
<tr>
<td></td>
<td>Anti-HTLV-I/HTLV-II (confirmatory and differentiation)</td>
<td>Second licensed HTLV-I/II ELISA, investigational Western blot</td>
<td>Avioq ELISA and MP Biomedicals, version 2.4 Western blot (outsourced)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Treponema pallidum Antibody (screen)</td>
<td>Hemagglutination assay for IgG and IgM antibodies</td>
<td>Beckman Coulter, PK TP PK7300 System</td>
</tr>
<tr>
<td></td>
<td>Treponema pallidum Antibody (confirmatory)</td>
<td>ELISA and RPR</td>
<td>Trinity Biotech Captia-G ELISA and Becton Dickinson Macro-Vue RPR Card Test</td>
</tr>
<tr>
<td>WNV</td>
<td>WNV RNA (screen)</td>
<td>TMA</td>
<td>Novartis PROCLEIX WNV</td>
</tr>
<tr>
<td></td>
<td>WNV RNA and Antibody (confirmatory)</td>
<td>TMA, PCR and IgM/IgG antibodies</td>
<td>Novartis PROCLEIX WNV; National Genetics Institute PCR and Focus Diagnostics IgM/IgG</td>
</tr>
<tr>
<td>Chagas</td>
<td>T. cruzi Antibody (screen)</td>
<td>ChLIA</td>
<td>Abbott (PRISM)</td>
</tr>
<tr>
<td></td>
<td>T. cruzi Antibody (confirmatory)</td>
<td>Enzyme Strip Assay (ESA) and Enzyme-linked immunoassay (EIA)</td>
<td>Abbott ESA and Ortho T. cruzi EIA</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Bacterial growth in culture</td>
<td>Bacterial aerobic media</td>
<td>bioMérieux BacT/ALERT 3D</td>
</tr>
</tbody>
</table>

^ Anti-HBc positive/HBsAg-negative samples are confirmed by HBV PCR with Roche COBAS Amplicscreen HBV test system

* Antibody-negative/RNA-positive samples are confirmed by polymerase chain reaction (PCR) at National Genetics Institute
## Appendix 5: Transfusion-Transmitted Infections (TTIs)

### 5A. Routine and Investigational Testing of Blood Donors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Prevalence in Blood Donors</th>
<th>Residual Risk for Recipient</th>
<th>Time Period</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 per 13,000</td>
<td>1 per 1,467,000</td>
<td>2006–2009</td>
<td>173–175</td>
</tr>
<tr>
<td>HCV</td>
<td>1 per 1,350</td>
<td>1 per 1,149,000</td>
<td>2006–2009</td>
<td>173–175</td>
</tr>
<tr>
<td>HBV</td>
<td>1 per 3,800</td>
<td>1 per 765,000–1,006,000</td>
<td>2006–2009, and 2009–2011</td>
<td>173, 176, 177</td>
</tr>
<tr>
<td>HTLV-I/II</td>
<td>1 per 40,938</td>
<td>1 per 4,364,000</td>
<td>2007–2008</td>
<td>172</td>
</tr>
<tr>
<td><em>Treponema pallidum</em></td>
<td>1 per 4,054</td>
<td>No transmissions reported since 1960s</td>
<td>2007–2008</td>
<td>173, 178</td>
</tr>
<tr>
<td>WNV</td>
<td>1 per 6,700–55,000 (varies by year) during transmission season</td>
<td>11 cases of transfusion transmission from screened blood; 1 case from granulocytes identified after transfusion as positive</td>
<td>June–Oct, 2003-2012</td>
<td>116, 135</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>1 per 38,500</td>
<td>No transmissions reported from screened blood; 20 cases of transfusion transmission reported in non-endemic areas globally</td>
<td>2007–2012</td>
<td>173,180, 181</td>
</tr>
<tr>
<td>Bacteria, Apheresis platelets</td>
<td>1 per 5,000</td>
<td>1 per 107,000 distributed components</td>
<td>2007–2012</td>
<td>182, 183</td>
</tr>
</tbody>
</table>
## Appendix 5: Transfusion-Transmitted Infections (TTIs)

### 5A. Routine and Investigational Testing of Blood Donors, continued

<table>
<thead>
<tr>
<th>Agent</th>
<th>Prevalence in Blood Donors</th>
<th>Residual Risk for Recipient*</th>
<th>Time Period</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria, WBD-pooled platelets (5 donors/pool)</td>
<td>1 per 1,200</td>
<td>ND</td>
<td>2008</td>
<td>184</td>
</tr>
<tr>
<td>Babesia microti (in endemic states RI, CT, MA)</td>
<td>1 per 200</td>
<td>6 transfusion transmissions from unscreened blood in CT/MA during the investigational testing</td>
<td>2012–2013 under IND in CT/MA</td>
<td>185, 186</td>
</tr>
<tr>
<td>Dengue virus (in Puerto Rico)</td>
<td>1 per 435</td>
<td>0 transfusion transmissions from screened blood</td>
<td>2012–2013 under IND in Puerto Rico</td>
<td>187</td>
</tr>
</tbody>
</table>

Abbreviations: WBD, whole blood-derived; ND, not determined

### 5B. Donor Screening Tests Not Routinely Used or Not Available

<table>
<thead>
<tr>
<th>Transfusion-Transmitted Infection</th>
<th>Estimated Incidence, Transfusion-Transmitted Infection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>1–4% with CMV reduced-risk components (seronegative donor or leukoreduced component)</td>
<td>138</td>
</tr>
<tr>
<td>Malaria (Plasmodia spp.)</td>
<td>RBC: &lt; 0.1 per 10⁶</td>
<td>188</td>
</tr>
<tr>
<td>Leishmaniasis (Leishmania spp.)</td>
<td>Rare case reports</td>
<td>189</td>
</tr>
<tr>
<td>vCJD</td>
<td>4 cases worldwide</td>
<td>190</td>
</tr>
<tr>
<td>CJD</td>
<td>None</td>
<td>191</td>
</tr>
<tr>
<td>Lyme disease (Borrelia burgdorferi)</td>
<td>None</td>
<td>192</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Red cells: 1 per 5,000,000 (Platelets: see Appendix 5A)</td>
<td>193</td>
</tr>
</tbody>
</table>
References


82. Package insert, Octaplas, Pooled Plasma (Human), Solvent/Detergent Treated Solution for Intravenous Infusion.


172. Schonewille H, van de Watering LMG, Brand A. Additional red blood cell alloantibodies after blood transfusions in nonhematologic alloimmunized patient cohort: is it time to take precautionary measures? Transfusion 2006;46:630–635.


