

# A Compendium of Transfusion Practice Guidelines

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## Introduction

Transfusion of blood products is one of the most common medical procedures, used for patients with a wide range of medical conditions to improve tissue oxygenation, achieve hemostasis, and/or fight infections. Moreover, transfusion therapy enables many complex procedures, such as organ transplantation, cardiac and other surgeries, and stem cell transplantation. Yet the curriculum of academic medical and nursing programs provide limited exposure and training towards helping providers to understand the attributes of the different types of blood products, appreciate the risks of transfusion, and raise awareness of the accumulating body of evidence that is helping to refine our understanding of clinical indications for each type of transfusion.

While the approach to transfusion medicine has historically been based on personal experience, local practice, expert opinion, and consensus conference recommendations, the availability of 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 provide a good foundation to develop evidence-based resources to aid in transfusion care of today and the future.

There is a growing belief that transfusion therapy, like many other types of drug therapies, can be tailored or personalized to address specific patient and disease contexts. One example is in the care of the actively hemorrhaging patient, particularly in the prehospital time frame. Though not yet supported by RCTs, there is a small but growing practice of utilizing cold-stored low titer group O whole blood containing functional platelets in lieu of balanced component therapy. The utility of other new products, such as cold-stored platelets, are also being actively debated in the actively bleeding population. In fact, clinical trials will soon be initiated to assess the feasibility and efficacy of low titer O whole blood and cold stored platelets in prehospital trauma and post complex cardiac surgery patients, respectively. In parallel, there are recent data to support reevaluating transfusion triggers for neonatal platelet transfusions and red cell transfusion triggers in outpatient settings for patients with chronic symptomatic anemia due to marrow failure. These examples highlight a shift in transfusion practice towards one in which specific use case scenarios (context of active bleeding, age, and/or inpatient vs. outpatient) define transfusion triggers or choice of blood product to ensure that transfusion therapy is optimized.

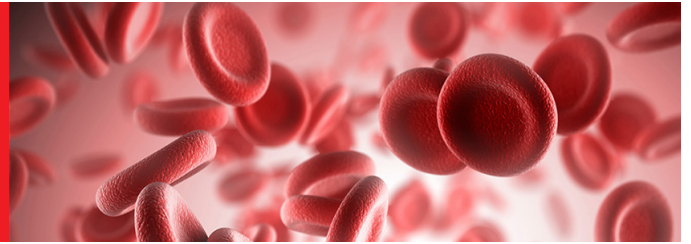
Transfusion safety continues to be the highest priority for our society and efforts to identify methods to reduce the risk of both known and emerging pathogens in all blood products are being investigated in current clinical trials. Pathogen reduction technology can successfully address infection risk from viral and bacterial pathogens. FDA approval of one such system, the INTERCEPT® System, for platelets and plasma has led to both increased availability and adoption of pathogen reduced (PR) platelets by blood centers and hospitals. Growth in the manufacturing of PR platelets has resulted in a concomitant increase in the use of platelet additive solutions such as PAS-C.

The concepts of patient-centered blood management (PBM) continue to be a major force in the health care community, with the focus of ensuring the right product for the right patient at the right dose and time. 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. This is supported by the results of the latest National Blood Collection and Utilization Surveys documented a continued decline of greater than 13% in both RBC and platelet transfusions between 2013 to 2015 but remained relatively unchanged between 2015 and 2017. However, variability in patient and laboratory parameters defining transfusion triggers between and within hospitals is still common, often reflecting hospital tradition as well as local and community practice. Moreover, despite the continued decline in overall RBC use, the use of group O negative RBCs continues to climb, putting pressure on a limited supply. In some hospitals, the use rate of O negative RBCs can be as high as 17-20%, suggesting a significant opportunity to standardize transfusion practices. National and local practice guidelines around appropriate transfusion triggers and use of universal blood products, such as group O negative RBCs, are powerful tools to minimize this variation and optimize clinical practice.

The importance of optimum transfusion practice is now under the purview of accrediting and regulatory agencies, such as The Joint Commission and AABB. 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. Regulatory agencies are also turning their attention to sustainability of the blood supply, specifically

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). This edition also highlights and expands on the emerging new products, such as low titer whole blood. Other changes include discussion on laboratory diagnostic testing support for transfusions and an overview of therapeutic apheresis services. The authors, all of whom are physicians or laboratory staff for the American Red Cross, have made every attempt to fairly reproduce the advice and lessons contained in these publications. Our hope is that this document will be a valuable resource to hospital staff who obtain blood components, diagnostic testing and therapeutic apheresis services from the American Red Cross as they develop and update their blood usage guidelines to help improve patient care.

# Red Blood Cells



## Components

Approved name:

- Red blood cells

Commonly used names:

- Packed cells
- Red cells
- Packed red blood cells
- RBCs

## Description <sup>(1-3)</sup>

Red Blood Cells (RBCs) consist of erythrocytes concentrated from a whole blood donation or collected by apheresis. They contain citrate anticoagulant and usually one of several types of preservative solutions. Depending on the preservative-anticoagulant system, the hematocrit (Hct) of RBCs is about 55-65% for additive solutions (AS), AS-1, AS-3, AS-5, AS-7 and about 65-80% for citrate-phosphate-dextrose-adenine solutions, CPDA-1, CPD, CP2D. RBCs contain 20-100 mL of donor plasma, but usually <50 mL, in addition to preservative and anticoagulant. The typical volume of AS RBCs including additive solution is 300-400 mL. Each unit contains approximately 50-80 g of hemoglobin (Hgb) or 160-275 mL of red cells, depending on the Hgb level of the donor, the starting whole blood collection volume, and the collection and processing methods. Leukocyte-reduced RBCs must retain at least 85% of the original RBCs. Each unit of RBCs contains approximately 250 mg of iron, almost entirely in the form of Hgb. This varies, of course, depending on the original volume and concentration of the unit.

## Selection and Preparation

Unless there is an urgent need for blood, RBCs should be compatible whenever possible with antibodies present in the recipient's plasma (on some occasions when a patient is multiply alloimmunized, a hospital might elect to transfuse over one of the antibodies if completely antigen-negative blood cannot be found). They must be crossmatched serologically or electronically, as applicable, to confirm this compatibility. Antibodies include naturally occurring isoantibodies anti-A and/or anti-B, (depending on the donor's blood type) and alloantibodies formed in response to red cell antigen exposure from pregnancy, a prior transfusion, or from the sharing of needles for injecting drugs. Some possible exceptions to the unit being completely crossmatch compatible may include:

- When an autoantibody is interfering with the initial crossmatch, but alloantibodies are identified and honored by using absorption techniques
- A clinically insignificant antibody is causing the incompatibility
- The (rare) emergency setting where the risk of patient morbidity/ mortality from the anemia outweighs the harm from a potential hemolytic reaction

This is not intended to be an exhaustive list of scenarios. Ultimately, the imminent clinical needs of the patient should always guide the decision to transfuse before the compatibility testing is completed or in the setting of an incompatible crossmatch.

In emergencies or during times of shortages, all transfusion services should have policies for using Rh(D) positive red cells in Rh-negative patients in order to conserve Rh(D) negative units for women of childbearing potential. Other groups that might warrant prioritization of D-negative blood are those who require chronic transfusion support (e.g. sickle cell disease), pediatric patients undergoing multiple surgical procedures, or patients destined for a stem cell transplant procedure, since all of these groups are more heavily transfused<sup>(4)</sup>. Rh positive units may be transfused to a Rh-negative male or female of non-childbearing potential who has not made anti-D, or whose D antigen type is unknown<sup>(4)</sup>. D-negative frequency is 17% in U.S. Caucasians, 7% in African-Americans and 2% in Asians<sup>(5)</sup>. However, these numbers are not always representative of ethnically diverse



populations. Anti-D is an incidental finding in a small percentage of blood donors. Studies have shown that 20-30% of Rh-negative hospitalized patients develop and have an anti-D after transfusion with a unit of RBCs<sup>(6-8)</sup>. However, the risk of an reaction due to emergently receiving an Rh incompatible unit is less than 1%, and even then the hemolysis is usually mild since it is extravascular<sup>(4)</sup>. Rates of alloimmunization in patients with AIDS and in transplant recipients is also lower. These immunosuppressed populations should be considered for switching to D positive blood when the need arises<sup>(4,9,10)</sup>. The same can be said of ER patients of non-child bearing potential who need urgent transfusion, as their chance of alloimmunization is as low as 3-6%<sup>(4)</sup>.

For women of childbearing potential for whom the Rh type is inconclusive or unknown, RHD genotyping is recommended to resolve the Rh(D) type. In the majority of Caucasians with a serologic weak D phenotype, RHD genotyping will reveal that the patient carries a weak D type 1, 2 or 3, for which the risk of alloimmunization to Rh(D) is known to be very low<sup>(11)</sup> and that Rh(D) positive blood may be used. In pregnant patients who are found to carry one of these three RHD variant alleles, Rh immunoprophylaxis is not necessary<sup>(12,13)</sup>. In 2016, a joint statement of the AABB, American Red Cross, College of American Pathologists, America's Blood Centers, American College of Obstetricians and Gynecologists, and the Armed Services Blood Program recommended RHD genotyping be used in women of childbearing potential to resolve serologic weak D phenotypes, or discrepant D types<sup>(14)</sup>. Some transfusion services have created criteria to identify patients that would benefit from RHD genotyping<sup>(15)</sup>.

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 for large volume transfusion to neonates may request that excess supernatant in transfusion aliquots be removed prior to administration, such as by centrifugation and volume reduction or by washing<sup>(2,16)</sup>.

## Age of Blood

The controversy over whether the transfusion of fresher RBCs results in fewer patient complications, compared to the use of older blood, has gone on for some time. But the debate was reinvigorated when a single-center retrospective study garnered intense media interest after publication by the New England Journal of Medicine in 2008<sup>(17)</sup>. This study by Koch et al, involving 6002 cardiac surgery patients, showed that recipients of red cells stored for more than 14 days had an increased incidence of adverse outcomes compared to those receiving cells stored for 14 days or less. Changes that can occur during storage of older blood were thought to be the cause<sup>(17)</sup>. However, other retrospective studies investigating the effect of red-cell storage duration on patients undergoing cardiac surgery showed no significant differences in outcomes.

Since release of the Koch paper, there have been several prospective, randomized clinical trials (RCTs) also looking at questions surrounding the age of stored RBCs. In developing their recent practice guidelines, AABB identified 13 RCTs involving more than 5000 patients and none of these studies suggested the use of older blood resulted in poorer patient outcomes<sup>(18)</sup>. For example, a study of 1098 patients undergoing cardiac surgery in more than 30 North American hospitals showed no statistically significant differences in multiple-organ dysfunction syndrome, adverse events, or 28-day mortality in groups receiving blood <10 days old (mean 7 days) vs. those receiving units exceeding 21 days of storage (mean 28 days)<sup>(19-22)</sup>. Another recent study in ICU patients, who were randomized to receive either "fresh" red cells (average 6 days old) vs. standard issue (average age 22 days), showed no difference in the primary end-point of mortality at 90 days<sup>(23)</sup>. Finally, one large multicenter trial enrolled 6,936 adults, with various diagnoses, to receive the freshest blood available (Mean storage duration: 13 days; median: 11 days) and compared them to 13,992 clinically-matched individuals who were transfused the oldest RBCs on the shelf (Mean storage duration: 23.6 days; median: 23) The investigators found no significant difference in overall mortality (9.1% vs 8.7%) between the 2 groups<sup>(24)</sup>.

Potentially vulnerable pediatric populations have also been analyzed. Premature infants weighing <1250 g did not demonstrate improved outcomes when receiving fresh RBCs (< 7 days old, mean storage= 5.1 days) vs. those given standard issue units (mean=14.6 days)<sup>(21)</sup>. A RCT involving 290 pediatric patients with elevated lactate levels, and hemoglobins of <5 g/dL found that children receiving RBC units stored for 1-10 days (median 8) had no significant reductions in lactate level or in adverse events versus those given units stored for 25-35 days, (median 32)<sup>(25,26)</sup>.

Based upon the studies described above, the 2016 AABB guidelines on the age of stored blood recommended that patients, including neonates, should receive red cells selected at any point within the licensed dating period, rather than limiting transfusions to only "fresh" blood (defined as RBCs <10 days old). The authors of this publication noted that most of the red cell storage trials they reviewed did not include neonates and children with underlying renal disease, patients with

serious hemoglobinopathies, nor anyone receiving massive or exchange transfusions or intrauterine transfusions. Hence, no recommendations were made for any of these groups<sup>(18)</sup>.

## General Information

### Dosing

RBCs should be transfused according to clinical need, including signs and symptoms, Hgb level, and the results of hematologic assays. In the absence of acute hemorrhage, RBCs should be given as single units followed by appropriate evaluation to justify additional units<sup>(27)</sup>. Transfusion of an RBC unit should be completed within four hours. If more time is required, smaller aliquots can be prepared and transfused sequentially.

### Response

In a non-bleeding, non-hemolyzing adult transfused with compatible RBCs, the hemoglobin level should equilibrate within 15 minutes of transfusion. One unit should increase the Hgb in an average-size patient (70-80 kg) by approximately one g/dL and the hematocrit by 3%<sup>(28)</sup>.

In neonates, a dose of 10-15 mL/kg is generally given, and additive solution red cells with a hematocrit 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 blood loss, hemolysis, or other processes that might affect in vivo survival. Seriously ill adult or pediatric patients may lose significant amounts of blood from phlebotomy for laboratory analysis<sup>(29)</sup>. In addition, when active bleeding is taking place, the anticipated post-transfusion hemoglobin level may be impacted by the dilutional effect of volume replacement with crystalloid or colloid.

### Indications and Contraindications

RBCs are indicated for patients with symptomatic deficiency of oxygen-carrying capacity, or tissue hypoxia due to inadequate circulating red cell mass. They are also indicated for exchange transfusions (e.g. in hemolytic disease of the fetus or newborn or for acute chest syndrome in sickle cell anemia etc.). Patients must be evaluated individually to determine the proper transfusion therapy, with care to avoid under- or over-transfusion. Transfusion decisions should be based on careful clinical assessment as well as Hgb levels<sup>(30)</sup>.

RBCs may be used for patients with acute blood loss whose symptoms or conditions may not improve with administration of crystalloid solutions. RBCs should not be used to treat anemia that can be corrected with therapies other than transfusion, such as pharmacologic agents. RBCs should also not be used as a means of increasing blood volume, to increase oncotic pressure, improve wound healing, or to improve a patient's sense of well-being.

For side effects and hazards, please see the Appendices.

## Utilization Guidelines

### Perioperative/Periprocedural

The function of an RBC transfusion is to augment O<sub>2</sub> delivery to the tissues. Hemoglobin levels during bleeding are imprecise measures of tissue oxygenation. Intravenous fluid resuscitation and the time needed for equilibration can significantly alter the Hgb concentration<sup>(31)</sup>. A number of factors besides blood Hgb level must be considered, such as pulmonary oxygenation, blood flow, Hgb O<sub>2</sub> affinity and tissue demands for O<sub>2</sub>(18,31,32). The Hgb level and clinical status of the patient should both be considered 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<sub>2</sub> levels, O<sub>2</sub> extraction ratios, or changes in oxygen consumption may be helpful in determining tissue oxygenation. Other factors to consider include anticipated degree and rate of blood loss, as well as the effect of body temperature or drugs and anesthetics on oxygen consumption. The American Society of Anesthesiologists Task Force (ASATF) recommends that RBCs should usually be administered when the Hgb concentration is low (for example, < 6g/dL in a young healthy patient), especially when the anemia is acute. Furthermore, the ASATF states RBCs are usually unnecessary when the Hgb concentration is >10 g/dL. These guidelines may be altered in cases of anticipated blood loss<sup>(32)</sup>.

The decision to transfuse should be based on any indication of organ ischemia, potential bleeding or the rate and magnitude of actual ongoing bleeding, the patient's intravascular volume status, and the risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption. The 2016 AABB guidelines state a restrictive transfusion threshold of 8 g/dL may be warranted in patients undergoing cardiac surgery or orthopedic surgery<sup>(18)</sup>.

Preoperative assessment and efforts to reduce RBC transfusion requirements in the perioperative period include the evaluation and treatment of anemia prior to surgery<sup>(31)</sup>. A recent international consensus conference on patient blood management recommended that screening for anemia be done well in advance of major elective surgery so that there is enough time to potentially manage it medically, thereby possibly reducing the need for perioperative transfusions<sup>(33)</sup>. The use of alternative measures to reduce allogeneic red blood cell use should also be considered. These include acute normovolemic hemodilution, intraoperative and postoperative autologous blood recovery, along with operative and pharmacologic measures that reduce blood loss.

The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines recommend the following be performed:

- Preoperative assessment to identify patients at elevated risk from bleeding (e.g. those of advanced age, or with decreased preoperative RBC volume, and those undergoing emergent or complex procedures), who may subsequently require blood transfusions
- Effective treatment of preoperative anemia and minimizing hemodilution during cardiopulmonary bypass (CPB) to preserve red blood cell volume,
- Appropriate management of preoperative antiplatelet and anticoagulant drug therapy, and the use of anti-fibrinolytic agents such as epsilon-aminocaproic acid or tranexamic acid to reduce total blood loss<sup>(34)</sup>.

## **Liberal vs. Restrictive Transfusion Thresholds**

Recent RCTs have consistently demonstrated the safety of using a restrictive threshold of 7 to 8 g/dL for most patients. As part of creating the 2016 AABB transfusion guidelines, a review and meta-analysis of 31 RCTs, involving a total of 12,587 subjects in various clinical settings (ranging from acute coronary syndrome to hematologic malignancies to orthopedic surgery, etc.) concluded that restrictive thresholds of 7-8 g/dL, when compared to 9-10 g/dL, were not associated with higher rates of adverse clinical outcomes such as 30-day mortality, cardiac morbidity and infection, with the exception of two small trials in subjects with acute myocardial infarction<sup>(35)</sup>. Furthermore, the lower transfusion threshold decreased the likelihood of receiving a PRBC exposure by 43% overall, and some studies showed survival was higher in certain patients who were transfused less: such as those with acute upper GI bleeding<sup>(36)</sup>.

However, caution is warranted before extrapolating this research on restrictive transfusion strategies to other patient groups that have yet to be studied, or where the data are extremely limited. Additional investigation is needed for those individuals with hematologic malignancies, or acute coronary syndromes or strokes before hemoglobin thresholds of 7 g/dL transfusions can be more routinely used in these patients<sup>(37)</sup>.

## **Cardiac Surgery**

Transfusions in cardiac surgery have been evaluated in randomized trials and suggest a Hgb threshold of 7.5 g/dL – 8 g/dL is acceptable in most cases<sup>(37,38)</sup>. The Transfusion Indication Threshold reduction (TITRe2) trial randomized 2007 patients undergoing coronary artery bypass graft (CABG), valve surgery, or both, to either a restrictive post-operative transfusion threshold of <7.5 g/dL or a liberal one of <9 g/dL. The composite primary endpoint of infection or an ischemic event was similar in both groups. Although more deaths were observed in the restrictive group at 90 days, the authors noted this was a secondary outcome and the events preceding death did not suggest a cause-and-effect relationship from anemia. Additionally, the 30-day mortality rate was similar in both cohorts<sup>(37,39)</sup>.

The Transfusion Requirements in Cardiac Surgery (TRICS) III trial, was an international, RCT conducted on almost 5,000 moderate to high-risk cardiac surgery patients on bypass. The investigators equally divided the subjects (2,430 patients in each arm) to be transfused either intraoperatively, or postoperatively in the ICU, only when the Hgb was <7.5 g/dL (intra-op or post-op) versus the liberal strategy which gave RBCs if it dropped below 9.5 g/dL<sup>(40)</sup>. Of note, the liberal transfusion threshold was made more restrictive (i.e. was lowered to 8.5 g/dL) once the patient was transferred to a non-ICU ward. The investigators concluded that the restrictive strategy was not inferior to the more liberal strategy based on the composite outcome of death

from any cause, myocardial infarction, stroke, or new-onset renal failure requiring dialysis. A follow-up to this study showed the restrictive strategy was still noninferior up to 6 months after surgery<sup>(41)</sup>.

Another study of CABG and valve surgery patients randomized 354 subjects to be transfused at a hematocrit of 28% and to withhold PRBCs from another 363 enrollees until their hematocrit dropped to 24%. No difference in the postoperative complications and lengths of stay was observed between the two groups, but there was greater blood product exposure to patients in the liberal arm<sup>(42)</sup>.

## General Critical Care

Individualization of red cell transfusion applies to critical care patients as well as perioperative patients. To the degree possible, the effects of anemia should be differentiated from those of hypovolemia, although both can impede tissue O<sub>2</sub> delivery. Blood loss greater than 30% of blood volume generally causes significant clinical symptoms and signs, but in younger healthy patients, resuscitation with crystalloids alone may be successful with blood loss of up to 40% of the patient's volume (approximately 2 liters of blood loss in an average adult male). Beyond that level of acute blood loss, even with adequate volume replacement, a normovolemic anemia will exist and the need to prevent a dilutional coagulopathy becomes even more important.

In otherwise healthy adults, adequate O<sub>2</sub> delivery is maintained at Hgb levels of 6-7 g/dL<sup>(32)</sup>. RBC transfusion should be strongly considered in critically ill trauma patients if, after adequate fluid replacement, the Hgb is < 7g/dL<sup>(30)</sup>. Tranexamic acid, an antifibrinolytic agent, may be helpful in trauma or surgical patients whose anemia is related to ongoing blood loss<sup>(43, 44)</sup>. RBC transfusion is indicated in patients with hemorrhagic shock and should be considered in patients with a Hgb < 7 g/dL who are on mechanical ventilation<sup>(30)</sup>.

A restrictive RBC transfusion strategy (Hgb < 7-8 g/dL) is recommended for hemodynamically stable, hospitalized, adult patients<sup>(18)</sup>. Several prospective studies demonstrated a higher mortality rate in patients receiving RBCs than in those not receiving them<sup>(45)</sup>. The TRICC (Transfusion Requirements in Critical Care) trial, published in 1999 was a multicenter RCT, comparing a transfusion trigger of 7g/dL with one of 9 g/dL in normovolemic critically ill patients<sup>(46)</sup>. Overall, 30-day mortality was similar in the two groups and in the subsets of more seriously ill patients, but the restrictive group received significantly fewer RBCs. For younger patients or those with a lower acuity level, the restrictive strategy resulted in lower 30-day mortality while decreasing RBC transfusions. The Transfusion Requirements in Septic Shock (TRISS) trial demonstrated that a Hgb threshold of 7g/dL was safe in patients with septic shock<sup>(47)</sup>.

In the setting of acute upper gastrointestinal (UGI) bleeding, a prospective, randomized, controlled trial comparing a liberal transfusion threshold (Hgb <9 g/dL) to a more restrictive one (<7 g/dL), clearly demonstrated reduced mortality at 45 days and a decreased rate of further bleeding in the restrictive threshold group. These improved outcomes occurred in patients with cirrhosis and Child-Pugh class A or B liver disease<sup>(36)</sup>. The liberal group's higher risk of bleeding was attributed to increases in splanchnic pressure caused by the transfused blood.

## Cardiovascular Disease

Although clinical trial data supports that many patient populations will tolerate withholding transfusions until the hemoglobin drops to 7 g/dl or lower, there is less data using this same threshold in patients with preexisting cardiovascular disease. For example, The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) randomized post-operative hip surgery patients with pre-existing cardiac disease or cardiovascular risk factors, to either a restrictive transfusion strategy (defined as a transfusion threshold of 8 g/dL or cardiac symptoms) or a liberal regimen using a threshold of 10 g/dL<sup>(48)</sup>. FOCUS found no significant differences, between the two groups in the frequency of in-hospital complications, the rate of death, or in the ability to walk on day 60. A Cochrane systematic review of the FOCUS study and five other trials in patients (n=2722) having hip fracture surgery also demonstrated a 8g/dl threshold to be safe<sup>(49)</sup>. A larger, subsequent, Cochrane database review analyzing patients from 31 RCTs with various of medical conditions also concluded it was still appropriate to transfuse at a hemoglobin of 8g/dl in clinical settings (e.g. in orthopedic surgery and in patients with cardiovascular disease) where the clinical data supporting a lower threshold was unavailable or insufficient<sup>(35)</sup>. Likewise, data is also lacking that provide guidance on when patients with acute coronary syndrome should be transfused<sup>(18,50)</sup>.

## Pediatric Critical Care

Infants may require simple or exchange transfusion for hemolytic disease of the fetus and newborn (HDFN), or for symptomatic anemia in the first months of life. The American Academy of Pediatrics has published guidance on specific indications for exchange transfusion in newborn infants at 35 or more weeks of gestation with hyperbilirubinemia, including that caused by HDFN<sup>(51)</sup>. Infants with jaundice caused by HDFN are at greater risk of bilirubin-related encephalopathy and are treated more intensively than infants with physiologic jaundice at any given unconjugated bilirubin level.

Apart from HDFN, neonatal anemia occurs mainly in preterm infants because of iatrogenic blood loss for laboratory testing, 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, however recent randomized studies support the use of a restrictive strategy<sup>(52-54)</sup>. In the multicenter PINT (Premature Infants in Need of Transfusion) study, 451 very low birth-weight infants were assigned to receive red cell transfusions using either restrictive or liberal criteria. Infants in the restrictive group had lower mean Hgb levels than those in the liberal group, and more infants avoided transfusion completely in the restrictive group (11%) compared to the liberal group<sup>(5%)</sup><sup>(54)</sup>. There was no difference between the two groups in composite outcomes of death, severe retinopathy, bronchopulmonary dysplasia, and brain injury, thus 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<sup>(52)</sup>. However, infants in the restrictive group were found to have more episodes of apnea and neurologic events than infants in the liberal group. A comparison of these studies suggests that the documented benefits of a restrictive transfusion practice are a decrease in the number of transfusions and exposure to fewer RBC donors. It is possible that the higher Hgb values maintained in the liberal transfusion group in Bell's study compared to the similar group in the PINT study may have decreased the risk of apnea and brain injury<sup>(54)</sup>.

A more recent meta-analysis of clinical trials comparing outcomes between restrictive vs. liberal hematocrit thresholds in neonates suggested that transfusion thresholds could be lowered, but identified the need for additional clinical studies to clarify the impact of this practice on long-term outcomes<sup>(55)</sup>. As for all pediatric patients, transfusion must take into consideration an infant's cardiorespiratory status, and transfusion decisions should be individualized for each patient.

### General Guidelines for Small-Volume (10-15 mL/kg) Transfusion in Infants<sup>(56)</sup>

- Severe cardiopulmonary disease with, e.g., mechanical ventilation with FiO<sub>2</sub> > 0.35: Hct < 40-45% (must be defined by institution)
- Moderate cardiopulmonary disease, e.g., less intensive assisted ventilation, such as nasal continuous positive airway pressure (CPAP) or supplemental O<sub>2</sub> therapies: Hct < 30-35%.
- Major surgery: Hct < 30-35%.
- Stable anemia, especially if unexplained poor growth or unexplained breathing disorder: Hct < 20-30%.

For older children, more likely to be treated in a pediatric ICU (PICU) setting, the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) recommended transfusing when the hemoglobin was less than 5g/dl for patients not in hemorrhagic shock; and between 5- 7 g/dl clinical judgement should guide transfusion decisions with a reasonable post-transfusion target being a hemoglobin of 7-9.5 g/dl<sup>(57)</sup>.

In hemodynamically stable children with hemoglobins exceeding 7 g/dl, transfusions were generally considered unnecessary, but might be beneficial in the following settings:

- Acute brain injury
- Acute respiratory distress syndrome
- Allo- or auto-immune mediated hemolytic anemia
- Cancer or hematopoietic stem cell transplant
- Cardiac disease
- Extracorporeal membrane oxygenation
- Ventricular assist devices



## Chronic Anemia

### Asymptomatic Chronic Anemia

Based on the specific diagnosis, treat with pharmacologic agents, 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 the Hgb is <6 g/dL, but this lower level is appropriate only for the healthiest and most stable of patients able to tolerate such a low red cell mass.

### 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 the treatment regimen or both<sup>(58)</sup>. The severity and duration of cancer-related anemia may vary with each malignancy's unique capability to suppress hematopoiesis, and with the specific chemotherapy used, This makes it difficult to develop a single set of RBC transfusion guidelines to cover all oncology patients .

This challenge is further compounded by the lack of clinical trials in the red cell literature looking at this patient population. A recent metanalysis identified 31 papers looking at restrictive versus liberal transfusion thresholds, but only 2 of those dealt with oncology patients and in both articles only subjects with hematologic malignancies were analyzed<sup>(35)</sup>. A 2017 Cochrane database review identified 4 more studies, one of which was not randomized<sup>(59)</sup>. All together this Cochrane Library publication found just 240 subjects for their analysis and thus were unable to draw any conclusions about the superiority of a restrictive transfusion policy.

Likewise, AABB did not make a recommendation for a transfusion threshold in oncology patients, nor did the National Cancer Network which urged physicians to use their clinical judgement based on patient symptoms, cancer course, treatment response, comorbidities and patient preference<sup>(18,60)</sup>.

### Sickle Cell Disease (SCD)

Evidence-based clinical guidelines and consensus statements have provided indications for transfusion in SCD<sup>(61)</sup>. As with most patients, but especially those who need chronic transfusion therapy, patients with SCD should receive leukoreduced red blood cells. The recent American Society of Hematology (ASH) 2020 Guidelines for SCD transfusion support ,written by Chou et al, conditionally recommended that extended RBC phenotyping (i.e. C/c, E/e, K, Jka/Jkb, Fya/Fyb, M/N, and S/s) be performed routinely on all SCD patients by either serologic or molecular methods<sup>(62)</sup>. Since peripheral blood DNA can be used to genotype recently transfused patients, without interference from donor cells, this is the preferred approach in a patient for which a baseline extended phenotype was not obtained prior to beginning their chronic transfusion protocol

Rh (E, C) and Kell warrant increased attention because they are particularly immunogenic. Alloimmunization and potential hemolytic transfusion reactions can be reduced by determining the antigen phenotype on the patient and prophylactic selection of antigen-negative RBCs, particularly those of the RhE, RhC and Kell phenotypes. In fact, the ASH guidelines strongly recommended that transfusions routinely be matched for these 3 antigens<sup>(62)</sup>. As patients are exposed over time to blood group antigens not expressed on their red blood cells, other antibodies to red blood cell group antigens may appear, and even more extensive matching may become necessary<sup>(63)</sup>. Increasingly, pediatric medical centers are performing or obtaining molecular RBC antigen typing (HEA and RH) for patients with SCD and are increasingly dependent on very rare donors who can supply antigen negative units<sup>(63-71)</sup>. Variant Rh antigens (D, C, c, e) and the loss of high prevalence Rh antigens (hrB, hrS, HrB, Hr) are common in individuals of African descent. Variant antigens should be considered in patients who express a Rh antigen and are found to have the corresponding antibody, or in those who develop Rh antibodies despite receiving C, E or C/c, E/e-matched RBC transfusions<sup>(63,64)</sup>. Transfusion of patients who are found to have made an antibody to a high prevalence Rh antigen such as hrB or hrS may be very difficult to manage; RH allele-matched donor units may be considered<sup>(72, 73)</sup>.

The choice between simple RBC transfusion and a red cell exchange (RCE) transfusion is generally based on clinical judgment and available resources. The therapeutic apheresis subsection of AABB recommends simple transfusions when symptoms are primarily due to anemia and the hemoglobin is less than 9 g/dL. Exchange transfusions may be more appropriate when the primary goal is decreasing the percentage of hemoglobin S to prevent or treat complications arising from vaso-occlusion, such as in acute stroke or in severe acute chest syndrome<sup>(74)</sup>. Automated RCE can achieve this without raising the hemoglobin above 10 g/dl where hyperviscosity can become more of a concern. If simple transfusions are being performed to improve anemia, care must be taken to avoid hyperviscosity<sup>(74)</sup>.

The National Heart, Lung, and Blood Institute (NHLBI) 2014 Evidence Based Management of Sickle Cell Disease Guidelines<sup>(61)</sup> recommend exchange transfusion for symptomatic severe acute chest syndrome (ACS) in patients with SCD. For other conditions such as acute splenic sequestration with severe anemia, aplastic crisis, and simple anemia, “simple” transfusion is recommended. Automated or manual RCE was also preferred over simple transfusions by the ASH panel for treating ACS but, like the most of their recommendations, this one was also conditional, based upon their review of the evidence<sup>(62)</sup>.

In preparation for surgery requiring general anesthesia, simple transfusion to increase the Hgb towards < 10 g/dL has been shown to be as effective as exchange transfusion in preventing complications, and resulted in lower blood usage and a lower rate of red cell alloimmunization dL<sup>(63)</sup>. However, RCE should be used in patients who are already between 9 and 10 g/dL preoperatively<sup>(63)</sup>.

A regimen of prophylactic transfusion therapy to maintain a Hgb S level below 30% of the total Hgb prevents stroke in high risk children with abnormal transcranial Doppler studies, and prevents recurrent stroke in those with a history of infarctive stroke<sup>(75, 76)</sup>. In a recent multi-center clinical trial, authors from several major institutions published a study on the preventive role of red cell transfusions in children with SCD and cerebral infarcts. Silent cerebral infarcts are the most common neurologic injury in such children and are associated with clinical stroke. In this three-year study, the investigators compared children receiving “standard therapy” to those receiving a monthly transfusion to keep the Hgb > 9 g/dL and Hgb S < 30%. maintaining a Hgb S level < 30%. The standard group received neither blood nor hydroxyurea therapy for silent infarcts. Transfused children had significantly fewer cerebral episodes and fewer other complications such as priapism, acute chest syndrome, vaso-occlusive pain and avascular necrosis of the hip, but no differences in cognitive ability were noted<sup>(77)</sup>. As expected, there were more transfusion reactions in the group that received blood and, longer-term, there may be higher rates of alloimmunization and iron accumulation.

The NHLBI and ASH recommendations for transfusion in SC reflect evidence-based reconsideration of previous practices or recommendations.<sup>(61, 62)</sup> In some clinical situations, the revised recommendations do not support automatic transfusion, for example, in uncomplicated painful crises, priapism, asymptomatic anemia, acute kidney injury without multi-system organ failure, and splenic sequestration. However, some patients may have better outcomes with exchange transfusion, which reduces the circulating volume of Hgb S erythrocytes and the potential for hyperviscosity. The decision to manage SCD with red cell exchange rather than simple transfusion should be made in consultation with an SCD clinical specialist. In contrast to simple transfusion, exchange transfusion utilizing cytapheresis prevented tissue iron accumulation and reduced iron overload in chronically transfused patients<sup>(78)</sup>.

The use of hydroxyurea, an oral alkylating agent which has been used in adults with SCD to promote increased fetal Hgb F levels, remains unclear in developing children. Hgb F retains higher levels of O<sub>2</sub> in the circulation, resulting in lower sickling rates in red cells. Additional investigation would be warranted to further define the management of SCD and how best to handle the multiple problems associated with SCD and transfusion<sup>(79)</sup>.

### **Evidence-based Recommendations for Transfusion in SCD<sup>(46)</sup>**

- Preoperative prophylaxis: children and adults, transfuse to 10 g/dl prior to general anesthesia:
- In SCD patients with Hgb > 8.5 g/dl on long term hydroxyurea or facing high-risk surgery (neurosurgery, cardiac bypass, prolonged anesthesia, for example), consult an SCD specialist.
- For patients not on long-term treatment with hydroxyurea and/or transfusion therapy who may have higher Hgb S and are at risk for hyperviscosity: avoid transfusion to hemoglobin > 10g/dl.
- Severe, symptomatic acute chest syndrome (O<sub>2</sub> sat. < 90% despite supplemental O<sub>2</sub> therapy)
- Acute splenic sequestration with severe anemia
- Children or adults with acute stroke (begin prophylactic transfusion regimen)
- Hepatic sequestration
- Intrahepatic cholestasis
- Multisystem organ failure
- Aplastic crisis
- Symptomatic anemia
- Child with transcranial Doppler reading > 200 cm/second
- Adults and children with previous clinically overt stroke

The more recent ASH guidance on managing SCD patients did overlap somewhat with the NHLBI 's recommendations, (e.g. on the topics of preoperative transfusion, transfusion of pregnant women and iron overload screening)<sup>(61, 62)</sup>. However, the 10 guidelines ASH developed, the only strong recommendation of the was on transfusing RBCs matched for the Rh (C, E or C/c, E/e) and K antigens. The other 9 recommendations were all conditional. By contrast NHLBI, graded the evidence regarding antigen matching as being of low quality, resulting in only a weak to moderate recommendation from their group. Of note, ASH also gave conditional recommendations (i.e. based on very low certainty in the evidence) to the use of isovolemic hemodilution with RCE, and to using immunosuppressive therapy for the prevention and treatment of hemolytic transfusion reactions.

## **Thalassemias**

Patients with some forms of alpha and beta thalassemia require frequent or chronic transfusion. These patients have been found to be at increased risk of alloimmunization to red cell antigens (16.5%)<sup>(80)</sup>. It is fairly common to obtain a red cell antigen phenotype by serology or HEA genotyping and select red cell products matched for RhC, RhE and K. Since peripheral blood DNA can be used to genotype recently transfused patients, without interference from donor cells, this is the preferred approach in a patient for which a baseline extended phenotype was not obtained prior to beginning their chronic transfusion protocol.

## **Oxygen Therapeutics (“Artificial Blood”, Oxygen Carriers)**

The acute need for blood for war and other violent conflicts, difficulties in acquiring, storing and testing blood, and the continuing global threat of emerging infectious diseases have driven efforts to find “blood substitutes.” There are currently no substances that perform all the functions of blood. An ideal oxygen therapeutic:

- Would circulate for a useful period of time
- Could be issued without crossmatching
- Could be easily stored for extended periods
- Would be capable of off-loading O<sub>2</sub> when required
- Could be easily be transported

Some of these criteria were met by products under development, but clinical trials identified adverse events. Several products were found to successfully circulate and deliver oxygen, but regulatory approval has not been given<sup>(81)</sup>. Complications included vasoconstriction, shock, and myocardial and cerebral infarcts. Further, it has been difficult to develop acceptable protocols for testing of these agents in trauma situations.

Several case reports have been published regarding the successful use of a conjugated, stabilized bovine hemoglobin solution in Jehovah's Witnesses with life-threatening anemia<sup>(82)</sup>. These infusions were approved by FDA on a case-by-case basis. A pegylated bovine Hgb solution appears to be of utility as a vasodilator, possibly helpful in various crises of SCD. Clinical trials are currently open. The effects of pegylated human tetrameric Hgb in vitro were reported in 2011 and further studies are underway<sup>(83)</sup>.

These products <sup>(82)</sup>, may be available for enhanced access (“compassionate use”) in life-threatening situations in patients for whom blood transfusion is not a conscience-based option. Obtaining these oxygen therapeutics requires close coordination among the requesting hospital, FDA, and the manufacturer. The FDA maintains 24/7 access to the emergency IND department for assistance to assist in obtaining an enhanced access product (866-300-4374). Information on current clinical trials and access to the Help Desk can be found on line at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## **Warm Autoantibodies and Interfering Immunologic Substances**

Warm autoantibodies are antibodies that react with substances on the patient's own red cells at body temperature. Presence of a warm autoantibody is usually associated with some kind of immunoregulatory dysfunction or infectious process and may or may not be associated with anemia or hemolysis. Red cells coated with autoantibodies presents challenges for antigen typing. Some facilities choose to match donor red cells for additional antigens. Immunotherapies such as anti-CD38 are showing significant efficacy in patients with multiple myeloma. While the monoclonal antibody binds to myeloma cells causing cell death, the antibody also binds to red cells interfering with antibody screening. Patients with warm autoantibodies as well as those receiving immunologic therapies that can act as interfering substances may benefit from utilization of HEA genotyping in predicting their red blood cell antigen phenotype.

## Red Cell Treatment Techniques prior to Antigen Typing

Immunohematology reference laboratories may use techniques such as EGA-treatment to remove antibodies from the surface of patient red cells followed by antigen typing. Such results should be interpreted with caution, since it has been shown that when compared to the red cell phenotype obtained by HEA genotyping panel, there can be false negative findings<sup>(84)</sup>.

Immunohematology reference laboratories may use hypotonic washing of a peripheral blood sample from a recently transfused patient with sickle cell disease, since the treatment will lyse the Hgb A cells leaving behind the Hgb S cells for antigen phenotyping. Such results should be interpreted with caution, since it has been shown that when compared to the red cell phenotype obtained by HEA genotyping panel, there can be false negative findings<sup>(84)</sup>.

## Red Cell Antigen Discrepancies

In cases where a current serologic type is discordant with a historic type, or a serologic type obtained in one laboratory is disagrees with another, or if one serologic reagent or method yields a result that is discordant with another reagent or method (including molecular methods), an investigation should be performed to resolve the discrepancy. Molecular methods such as genotyping using an HEA panel or higher resolution molecular methods such as Sanger sequencing can identify variant alleles that may encode weakened or partial antigens that react differently based on the reagent or method used. These techniques may also reveal that the patient carries a null allele that does not express the antigen. Resolution of the discrepancy may eliminate the need for antigen negative red cell products and in some cases may uncover partial antigens that put the patient at risk for alloimmunization.

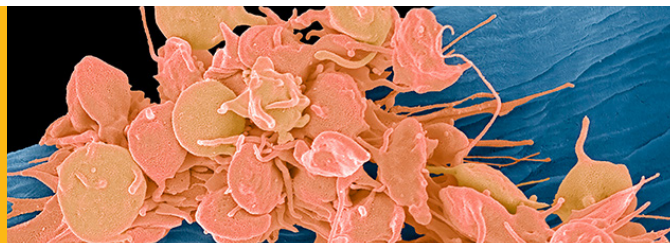
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# Platelets



## General Information

### Components

Approved names:

- Platelets
- Platelets Pooled Platelets (Platelets Pooled)
- Platelets Leukocytes Reduced
- Pooled Platelets Leukocytes Reduced (Platelets Leukocytes Reduced, Pooled)
- Apheresis Platelets (Platelets Pheresis)
- Apheresis Platelets Leukocytes Reduced (Platelets Pheresis Leukocytes Reduced)
- Apheresis Platelets Platelet Additive Solution Added Leukocytes Reduced (Platelets Pheresis Platelet Additive Solution Added Leukocytes Reduced)

Commonly used names:

- Platelets
- Single Donor Platelets (SDP)
- Platelet Additive Solution (PAS) Platelets/PAS Platelets
- Random Donor Platelets (RDP)
- Pooled Platelets
- PSP
- Pathogen-Reduced (PR) Platelets

### Description of Basic Components

Apheresis platelets are collected from a single donor using automated devices known as cell separators. These products are often called Single Donor Platelets (SDPs) and contain  $\geq 3.0 \times 10^{11}$  platelets (average  $3.5\text{--}4.0 \times 10^{11}$ ) per unit in approximately 100–500 mL of plasma or plasma with platelet additive solution (PAS). The anticoagulant used is acid citrate dextrose (ACD). Approximately 93% of platelet transfusions are apheresis platelets<sup>(1)</sup>.

Platelets derived from whole blood contain  $\geq 5.5 \times 10^{10}$  platelets per bag (unit) in 40–70 mL of plasma. The anticoagulant is the same as that used for whole blood collection, usually citrate phosphate dextrose (CPD) or citrate phosphate 2 dextrose (CP2D). They are often referred to as random donor platelets (RDPs) to distinguish them from SDPs. Four to six units are often pooled by the blood center or hospital to make an adult dose that can be estimated by multiplying the number of RDPs in the pool by the required minimum number of platelets,  $\geq 5.5 \times 10^{10}$ , in each whole blood-derived unit. They may be used as single units for pediatric patients.

Platelets in platelet additive solution (PAS) are Apheresis Platelets Leukocytes Reduced and are suspended in a mixture of plasma and proprietary additive solutions. In two additive solutions that have been cleared for use in the United States, the platelet suspension contains approximately 35% residual plasma and 65% PAS<sup>(2)</sup>. Plasma proteins, including ABO isoagglutinins, coagulation factors, and allergenic substances, are diluted in proportion to the PAS added. The shelf life of Apheresis Platelets Leukocyte Reduced in PAS is 5 days, and they may be further processed (e.g., irradiated or aliquoted). Retrospective clinical comparison of PAS platelets to those suspended in 100% plasma demonstrated a reduction in allergic transfusion reactions<sup>(3)</sup>. In this study, circulation of transfused platelets in PAS, as measured by the corrected count increment (CCI) immediately after transfusion, was lower compared to those suspended in 100% plasma, but not significantly different when measured 12 to 24 hours after transfusion. In another retrospective study, patients transfused with platelets suspended in additive solution experienced fewer febrile reactions and allergic reactions than those transfused with platelets in 100% plasma.<sup>(4)</sup>

A psoralen and ultraviolet light-based pathogen reduction process for leukocyte reduced Apheresis Platelets in PAS and leukocyte reduced Apheresis Platelets in plasma have been implemented in several US blood centers. The shelf-life of pathogen reduced apheresis platelets is 5 days. Pathogen reduced apheresis platelets do not require testing for bacteria <sup>(5)</sup>, CMV <sup>(6)</sup>, Babesia <sup>(7)</sup>, or Zika <sup>(8)</sup>, and do not require gamma irradiation as prophylaxis against transfusion-associated graft versus host disease in susceptible recipients <sup>(6)</sup>. A meta-analysis of clinical trials of psoralen-based pathogen reduced platelets revealed no significant differences in mortality or bleeding of platelets receiving pathogen reduced platelets and those receiving standard platelets <sup>(9)</sup>.

In September 2019, the Food and Drug Administration issued Final Guidance for the industry to address bacterial contamination risk reduction <sup>(10)</sup>. Several methods were provided to meet the guidance objectives including pathogen reduction, large volume—delayed sampling (LVDS) at greater than 36 or 48 hours after collection, primary culture followed by secondary culture, and point of issue testing (see FDA Final Guidance for details). The LVDS testing methodology involves holding apheresis platelets until at least 36 or 48 hours have elapsed from collection then obtaining a 16-20 mL sample from each final split product for aerobic and anaerobic culture. This longer period between collection and sampling as well as the larger aliquot drawn for testing increases the likelihood of bacterial detection <sup>(11)</sup>.

*Leukoreduction standards are discussed in the Blood Component Modification chapter*

## Preparation of Platelets

An “apheresis platelets” product is considered to be one adult dose. To prepare an adult dose of pooled platelets, 4-6 RDPs are pooled by the blood center or hospital prior to transfusion. When prepared and pooled using an FDA-approved system, the post-collection shelf life is 5 days.

## ABO and Rh Compatibility

Donor plasma in platelets suspended in plasma should be ABO-compatible with the recipient's red cells. This is particularly important when transfusing infants or giving large volumes to adults, to avoid the possibility of exposure to potentially hemolyzing isoagglutinins (anti-A and/or anti-B).

Rh-negative recipients should receive Rh-negative platelets when available, particularly women of childbearing age. However, apheresis platelets may contain a very small volume of RBCs (up to 0.001 mL), and it has been suggested that Rh immune prophylaxis may not be necessary when Rh positive platelets are given to Rh negative patients <sup>(6)</sup>. In a study that included hematological, oncological and patients with other conditions, D alloimmunization by Rh(D) positive apheresis platelets given to Rh(D) negative recipients was reported to be approximately 1.4% after a median 77 day follow up <sup>(13)</sup>.

## Dosing

Clinical practice guidelines for prophylactic and therapeutic platelet transfusion have been recently published and are based on systematic literature review and recommendations using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework <sup>(14,32)</sup>.

To treat bleeding or prepare patients for invasive procedures, transfuse as needed to maintain hemostasis or the target platelet count, whichever is applicable. Four to ten units of RDPs, one to two units of Pooled Platelets (each containing approximately 4 to 6 whole blood platelet concentrates), or one to two SDPs are generally transfused to thrombocytopenic or thrombocytopathic adults. The Prophylactic Platelet Dose on Transfusion Outcomes (PLADO) trial concluded that prophylaxis at pre-specified triggers was accomplished with equivalent effect on hemorrhage, using three RDPs or half of an SDP in adults, provided that the minimum dose exceeded  $1.1 \times 10^{11}$  platelets per square meter of the patient's body surface area. This strategy, however, resulted in more frequent transfusions, usually on a daily basis <sup>(15)</sup>. A higher minimum dose of  $2.4 \times 10^{11}$  platelets per square meter for outpatients is likely to be more cost effective, minimizing the number of patient visits <sup>(16)</sup>. It is recognized that in the lowest dosing arm of the PLADO study, the dose of platelets given was  $<3 \times 10^{11}$ /unit and would not meet current minimum standard dose for platelets in the US. However lower standard minimum doses are used in Canada and other European countries <sup>(17)</sup>.

## Response

Recipient response to platelet transfusion can be measured by the count increment (CI), which is defined as the increase in platelet count, measured in platelets/ $\mu$ L usually 10-60 minutes, after transfusion (a “one hour” post transfusion platelet count).

The CI is measured by subtracting the pre-transfusion platelet count from the post-transfusion platelet count and is a simple method to judge response to platelet transfusion. For an adult of 70 kg, the platelet CI should be approximately 5,000–10,000/ $\mu\text{L}$  for each RDP or 10,000–60,000/ $\mu\text{L}$  for each SDP given. In neonates and infants, a dose of 5–10 mL/kg of platelets should result in a 50,000–100,000/ $\mu\text{L}$  increment<sup>(18-20)</sup>.

Although the CI takes into account the dilutional effect of transfusion, a more accurate calculation for response to platelet transfusion is the corrected count increment (CCI), which also includes correction for body surface area and the number of platelets transfused:

$$\text{CCI} = \text{CI} \times (\text{body surface area in m}^2) / \text{number of platelets transfused (} \times 10^{11} \text{)}$$

As an example, for a person with a BSA of 1.8 m<sup>2</sup> and a platelet count increment (CI) of 15,000/ $\mu\text{L}$  after a transfusion with  $3 \times 10^{11}$  platelets, the CCI would be  $(15,000 \times 1.8/3) = 9,000$ . Generally, CCIs measured between 10 and 60 minutes post-transfusion are expected to be  $>7,500$ , and reflect 20–30% platelet recovery due to normal platelet consumption to support endothelial function. Platelet refractoriness is defined as a  $\text{CCI} \leq 7,500$  for at least 2 sequential platelet transfusions<sup>(21)</sup>. Refractory platelet transfusions can be due to a number of non-immune causes, including fever, infection, bleeding, DIC, extensive surgery, splenomegaly, irradiation, and concurrent amphotericin B therapy<sup>(22)</sup>.

Failure to achieve the expected response within one hour of transfusion suggests the existence of HLA alloimmunization or immunization to human platelet antigens (HPA). In the absence of a consumptive process or decreased production, post-transfusion counts may be somewhat lower than the dose administered because approximately 7,100 platelets/ $\mu\text{L}$  are consumed daily in endothelial support functions, the equivalent of approximately one RDP per day for a 70 kg adult with marrow failure<sup>(23)</sup>.

## Indications

Use to treat bleeding due to critically decreased circulating platelet counts or functionally abnormal platelets. Use prophylactically to prevent bleeding at pre-specified low platelet counts. In general, maintain platelet count at  $>10,000/\mu\text{L}$  in stable, non-bleeding patients, at  $>20,000/\mu\text{L}$  in unstable, non-bleeding patients, and at  $>50,000/\mu\text{L}$  in patients who are actively bleeding or undergoing major invasive procedures or surgery.

## Contraindications

Use of platelets in patients with autoimmune thrombocytopenia, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), idiopathic thrombocytopenic purpura (ITP), or heparin-induced thrombocytopenia with thrombosis (HITT) should be avoided except for life-threatening hemorrhage. Transfusion before invasive procedures or surgery in patients without thrombotic manifestations may be considered when the risk of bleeding is high<sup>(24,25)</sup>.

*For side effects and hazards, please see the Appendices. For information on pathogen-reduced platelets and plasma please refer to the Blood Component Modification chapter.*

## Utilization Guidelines

### Surgery

- Prophylactic preoperative transfusion is rarely required for counts  $>100,000/\mu\text{L}$ , is usually required for counts  $<50,000/\mu\text{L}$ , and is guided by risk factors for intermediate counts<sup>(26)</sup>.
- Intraoperative platelet counts should be obtained to guide transfusion
- Procedures with insignificant blood loss or vaginal deliveries can be performed at counts  $<50,000/\mu\text{L}$  without prophylactic transfusion.
- Transfusion may be required with apparently adequate counts when known or suspected platelet dysfunction results in microvascular bleeding.
- Point of care (POC) testing devices, which reflect the availability of functional platelets and/or coagulation and fibrinolytic proteins, can assess hemostatic function in bleeding surgical patients and during massive transfusion situations. These tests can guide optimal administration of blood products and reduce inappropriate component utilization<sup>(27-29)</sup>.



## Cardiothoracic Surgery

Routine prophylactic transfusions do not alter bleeding or postoperative transfusion requirements and are not recommended for non-thrombocytopenic patients. There are no published guidelines for managing patients on aspirin and P2Y12 receptor inhibitors and other anti-platelet drugs. These patients are known to be at higher risk for bleeding and reoperation, however, management of patients taking these agents may require platelet transfusions in urgent situations<sup>(30,31)</sup>. Platelet transfusion is recommended for patients who are on cardiopulmonary bypass for cardiovascular procedures and who exhibit microvascular perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction<sup>(32)</sup>.

### Specific Procedures

- When pre-procedural transfusion is deemed necessary, a post-transfusion count should be obtained to assure an appropriate increment prior to the procedure.
- In the absence of coagulopathy or thrombocytopathy, AABB clinical practice guidelines suggest “prophylactic platelet transfusion for patients having major elective non-neuraxial surgery with a platelet count less than  $50 \times 10^9$  cells/L”<sup>(32)</sup>. Procedures including paracentesis/thoracentesis, liver biopsy, sinus aspiration, and dental extraction may also require platelet transfusion.
- The AABB suggests “prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than  $20 \times 10^9$  cells/L”<sup>(32)</sup>. Serious bleeding complications after CVC placement are rare and are usually due to complications rather than thrombocytopenia<sup>(15)</sup>.
- The AABB suggests “prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than  $50 \times 10^9$  cells/L”<sup>(32)</sup>. Studies evaluated for development of these guidelines, however, included adult and pediatric patients, and showed no bleeding complications at platelet counts less than  $50 \times 10^9$  cells/L or less than  $20 \times 10^9$  cells/L. Consideration may be given to reserving the higher threshold for high-risk lumbar puncture, noting potentially enhanced safety at counts above  $20,000/\mu\text{L}$ <sup>(33-35)</sup>.
- A threshold of  $80,000/\mu\text{L}$  has been proposed for spinal and epidural anesthesia. Neurologic or ophthalmologic procedures may require a platelet count near  $100,000/\mu\text{L}$ <sup>(19)</sup>.
- Fiberoptic bronchoscopy or GI endoscopy without biopsy may be safely performed by experienced operators in the presence of a platelet count  $<20,000/\mu\text{L}$ .
- Bone marrow biopsy may be safely performed with counts at or below  $10,000\text{--}20,000/\mu\text{L}$ <sup>(19,35)</sup>.

### Prophylactic PLT Transfusion Thresholds <sup>(32)</sup>

Procedure	PLT/ $\mu\text{L}$
Major elective non-neuraxial surgery	50,000
Venous catheter placement	20,000
Spinal and epidural anesthesia	80,000
Flexible bronchoscopy or GI endoscopy	20,000–50,000
Bone marrow biopsy	10,000–20,000

### 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. The underlying condition should be managed when at all possible to avoid platelet transfusion, for example, the administration of desmopressin acetate (DDAVP) in uremia or plasma exchange for hyperglobulinemia, which are more efficacious treatment options. When platelet surface glycoproteins are absent, as in Glanzmann thrombasthenia or Bernard-Soulier syndrome, transfusion should be undertaken only when more conservative efforts to manage bleeding have failed, since alloimmunization due to repeated transfusion 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 in the absence of thrombocytopenia, but high-dose therapeutic transfusion may be required for life-threatening hemorrhage in patients on these drugs<sup>(30,31)</sup>.

## Massive Transfusion

There is no consensus on the definition of massive transfusion<sup>(36)</sup>. The platelet count may fall below 50,000/ $\mu$ L when >1.5–2 blood volumes have been replaced with red cells or other components. A transfusion target of  $\geq$ 50,000/ $\mu$ L is recommended for acutely bleeding patients and  $\geq$ 100,000/ $\mu$ L for those with multiple trauma or CNS injury<sup>(37)</sup>. In the presence of microvascular bleeding, transfusion may be appropriate when counts are known or suspected to be <100,000/ $\mu$ L. Early aggressive platelet therapy has been associated with improved survival in several retrospective studies<sup>(38)</sup>.

## Disseminated Intravascular Coagulation (DIC)

Transfusion is appropriate in children and adults with platelet counts <50,000/ $\mu$ L who have active bleeding, require an invasive procedure, or are otherwise at high risk for bleeding complications<sup>(39)</sup>.

## Pediatrics<sup>(40,41)</sup>

Neonates undergoing invasive procedures or surgery or experiencing clinically significant bleeding may be transfused at <50,000/ $\mu$ L. A prophylactic transfusion trigger of <20,000/ $\mu$ L for stable neonates at term, or <30,000/ $\mu$ L for stable premature neonates, is justified. High-risk neonates (those with extremely low birth-weight, perinatal asphyxia, sepsis, ventilatory assistance with an FIO<sub>2</sub> >40%, or clinical instability) may be transfused at <30,000/ $\mu$ L at term or at <50,000/ $\mu$ L 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/ $\mu$ L.

## Oncology

Platelets should be transfused prophylactically to patients with a platelet count of  $10 \times 10^9$  cells/L or less to reduce the risk of spontaneous bleeding in hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia. AABB guidelines emphasize transfusing a single apheresis unit or equivalent. Additional transfusions are not more effective<sup>(32)</sup>. Prophylactic platelets may be given despite a higher platelet count if clinical factors such as drug-induced platelet dysfunction, fever and/or sepsis, hyperleukocytosis, tumors with greater risk of hemorrhage, use of antithymocyte globulin, acute graft-versus-host disease, or hepatic veno-occlusive disease are present. Results from a 14 center, randomized, open-label, non-inferiority trial conducted in the United Kingdom and Australia support the continued use of prophylactic platelet transfusion to reduce bleeding as compared to no prophylaxis<sup>(42,43)</sup>.

## Intracranial Hemorrhage in Patients on Antiplatelet Agents (traumatic or spontaneous)

There are no clear guidelines for transfusion in patients on antiplatelet agents with intracranial hemorrhage. Clinical factors such as the extent of hemorrhage, type of procedure planned, and the patient's level of consciousness may inform the decision to transfuse<sup>(31)</sup>.

## Platelet Refractoriness<sup>(44–48)</sup>

Platelet refractoriness may be due to immune or non-immune causes and should be suspected after two or more poor responses to transfusion. The most common cause of immune refractoriness is the presence of HLA antibodies and, less frequently, antibodies to human platelet antigens (HPA), which can be confirmed by the demonstration of HLA or HPA antibodies, respectively. Post-transfusion platelet counts obtained 10–60 minutes after infusion should be obtained whenever transfusion refractoriness is suspected. To judge survival when refractoriness is suspected, it is equally important to obtain an immediate pre-transfusion count.

When possible, ABO identical units should be used<sup>(49)</sup>. Successful transfusion is defined as a CCI  $\geq$ 7,500. This specific calculation may not always be warranted, as refractory patients typically have a one-hour post count increment of less than 5000/ $\mu$ L; such a finding suggests HLA alloimmunization as the likely cause of refractoriness. Post-infusion counts at 24 hours assess platelet survival, which is sensitive to non-immune and immune conditions.

For patients suspected to be refractory due to alloimmunization, there are a few options for transfusion. Many algorithms exist for obtaining appropriate platelets for these patients. Early consultation with the transfusion service medical director is essential prior to initiating the process of obtaining these special products<sup>(49,50)</sup>.

The available options will largely be determined on the urgency of transfusion and the type of testing already performed on the patient's sample. HLA and HPA typing of patients is performed using molecular methods (see Patient Testing section) HLA and HPA antibody detection can be performed with serologic assays with detection by ELISA, Solid Phase or Flow Cytometric

methods. HLA and HLA antibody specificities are commonly determined by flow-based assays. HLA antibody identification using flow cytometric bead-based testing can further provide specific information as to the nature of the antibodies resulting from alloimmunization of the patient. Platelet products that are HLA/HPA-matched or HLA/HPA compatible (i.e. products lacking antigens to antibodies detected in the patient) may then be selected for patient transfusion. If patient testing for HLA/HPA type and HLA/HPA antibodies is not available, then platelet crossmatching is an option to find potentially compatible units while awaiting further patient testing.

HLA matched platelets must undergo gamma or x-ray irradiation or pathogen reduction to prevent transfusion-associated graft versus host disease (TA-GVHD).

A meta-analysis of psoralen and ultraviolet light-based clinical trials demonstrated that the relative risk of platelet refractoriness (low CCI's in two successive transfusions) was 2.74-fold greater in pathogen reduced platelets than standard platelets<sup>(6)</sup>. Patient receiving pathogen reduced platelets in this meta-analysis required 7% more platelet transfusions.

### **Idiopathic Thrombocytopenic Purpura (ITP)<sup>(51)</sup>**

Patients who experience major, life-threatening bleeding or intraoperative hemorrhage should receive high-dose platelet transfusions as well as steroids, intravenous immunoglobulin (IVIG), and any other appropriate second-line therapies. Prophylactic transfusions are usually inappropriate since transfused platelets do not survive any longer than the patient's own platelets. Administration of IVIG may be considered before minor surgery with platelet counts  $\leq 50,000/\mu\text{L}$  or major surgery with counts  $\leq 80,000/\mu\text{L}$ .

### **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<sup>(24,25)</sup>.

### **Post-transfusion Purpura (PTP)**

IVIG is the treatment of choice for PTP. Platelets may be administered for severe bleeding, but transfusion of platelets is usually ineffective unless the patient lacks the specific platelet antigen. Though efficacy is not well documented, HPA-1a-negative platelets, if available, are frequently given empirically pending specific alloantibody testing results, as 70% of cases of PTP are due to HPA-1a antibodies. Washed or deglycerized red cells should be given if a red cell transfusion is indicated.

### **Neonatal Alloimmune Thrombocytopenia (NAIT)<sup>(51)</sup>**

While awaiting a response to IVIG, platelet transfusions are indicated for severe thrombocytopenia and/or bleeding. Ideally, platelets should be selected that lack the HPA recognized by circulating maternal antibodies<sup>(52)</sup>. Molecular typing of patient platelets is used to determine the HPA phenotype, in NAIT and is typically performed using an HPA genotyping panel<sup>(53)</sup>. Until HPA selected platelets are found, HPA non-selected platelets have been shown to meet the clinical need [ICTMG paper]. 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 with NAIT are assumed to have exposure to HPA-1a antibodies.

### **Aplastic Anemia**

Transfuse stable patients prophylactically at counts  $\leq 5,000/\mu\text{L}$  and patients with fever or minor hemorrhage at counts  $6,000\text{--}10,000/\mu\text{L}$ <sup>(54)</sup>.

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# Low Titer Group O Whole Blood



## General Information

Approved Names:

- Low Titer Group O Whole Blood
- Whole Blood
- Heparin Whole Blood
- Whole Blood, antihemophilic factor removed

Commonly Used names:

- Low titer Group O whole blood
- Whole blood
- Leukocytes reduced whole blood
- Leukocytes reduced low titer whole blood
- Leukocytes reduced low titer TRALI mitigated whole blood

## Description

Low titer group O whole blood (whole blood) is collected into approved Blood bags made of polyvinyl chloride (PVC), which are plasticized with diethylhexyl phthalate (DEHP). Each unit contains a fixed amount of anticoagulant, which is specified on the label. Whole blood must be cooled towards 1--10°C as it is transported from the collection site, and must be stored at 1-6°C<sup>(1)</sup>. The expiration of the whole blood unit is based on the anti-coagulant into which it is drawn. In practice, transfusing physicians may limit the use to a time period shorter than the approved expiration (see History and Current Utilization, below). The 31st edition of the AABB Standards for Blood Bank and Transfusion Services no longer requires whole blood to be ABO identical.

## Selection and Preparation

Whole blood must be tested for the presence of all required infectious disease markers, and the ABO type must be confirmed by forward and back typing and undergo standard testing for the Rh type and RBC antibody screen. In practice, transfusing physicians may limit WB use to a time period shorter than the approved expiration (see History and Current Utilization below). The 31st edition of the AABB Standards for Blood Bank and Transfusion Services no longer requires whole blood to be ABO identical if low-titer group O whole blood is used in a manner consistent with the current standards<sup>(2)</sup>. The use of a leukoreduction filter may also spare the majority of platelets, although no labeling language is approved to denote the presence of active platelets in the unit of whole blood. If platelet sparing leukofiltration is performed, the whole blood must undergo leukocyte reduction in accordance with the manufacturer's instructions for use, typically within eight hours of collection. The relative abundance of isohemagglutinins, determined either from a concurrently drawn blood sample or from a segment from the collected whole blood unit, may be determined. This information can be used as a release criterion, with only units found to have a titer less than a pre-determined cut-off able to be labeled for final distribution as whole blood. This information is not reflected on the label but may be included on a tie tag. AABB standards identify whole blood as a high plasma product and require it to be appropriately TRALI risk mitigated<sup>(2)</sup>.

## History and Current Utilization

From the early days of Transfusion pioneers such as James Blundell, MD<sup>(3)</sup> and Lieutenant Oswald Hope Robertson, MD<sup>(4)</sup>, whole blood has been administered to provide lifesaving resuscitation to rapidly exsanguinating patients. The development of blood component manufacturing technologies, particularly the introduction of plasticized polymer blood bags during the Korean war<sup>(5)</sup>, led to the use of a variety of blood components to provide specific replacement of varying blood constituents across the clinical spectrum. Research into optimal resuscitation of patients with massive bleeding from trauma was once again advanced

by the experience of physicians treating soldiers. Initially insights provided evidence into the ratio of Transfusion of conventional components<sup>(6)</sup> while advocacy for return to the use of whole blood also grew<sup>(7)</sup>.

## Massive Hemorrhage Associated with Trauma

In military<sup>(8)</sup> and civilian<sup>(9)</sup> settings, whole blood from group O donors has been introduced as the preferred initial intervention to address trauma associated massive hemorrhage. Low titer group O whole blood (LTOWB) may be used to replace the initial massive Transfusion pack, as this product provides red cells, plasma and platelets in a nearly physiologically representative unit. AABB Standards require hospitals track ABO incompatible plasma Transfusion<sup>(2)</sup>. Some hospitals perform a direct antiglobulin test (DAT) after a patient has received more than a pre-determined volume of incompatible plasma. However, published studies to date have not demonstrated that LTOWB is associated with hemolysis in civilian trauma patients<sup>(10)</sup>. The design for a prospective randomized trial comparing fresh whole blood to traditional blood components has been published<sup>(11)</sup>.

## Pediatric Open-Heart Surgery

The use of whole blood in pediatric cardiothoracic surgery has been debated for many years. Recent evidence<sup>(12)</sup> continues to suggest that Transfusion needs - and the concomitant risk of adverse reactions from multiple donor exposures - can be reduced in these cases by the use of fresh whole blood. The value of functional platelets in whole blood processed with platelet sparing leukocytes reduction filters has not yet been fully characterized.

## Non-trauma associated hemorrhage

The appropriateness of using whole blood in civilian settings, particularly in non-trauma or routine surgical settings has not been determined, and randomized control trials to compare outcomes with component therapy vs. whole blood are warranted as evidenced based Transfusion therapy continues to advance<sup>(13, 14)</sup>. Limited data<sup>(15)</sup> suggests a clinical benefit in obstetrical bleeding, while no significant data are available for other common causes of non-traumatic massive bleeding, such as gastrointestinal or urogenital or adult cardiovascular procedures.

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# Plasma



## General Information<sup>(1, 2)</sup>

### Components

Approved names and abbreviations:

- Fresh Frozen Plasma (FFP)
- Plasma Frozen within 24 hours after Phlebotomy (PF24)
- Plasma Frozen within 24 Hours after Phlebotomy Held at Room Temperature up to 24 Hours after Phlebotomy (PF24RT24)
- Thawed Plasma (“Thawed Plasma”)
- Liquid Plasma (“Liquid Plasma”)
- Plasma Cryoprecipitate Reduced (“Plasma, Cryoprecipitate Reduced”)
- Thawed Plasma Cryoprecipitate Reduced (“Thawed Plasma, Cryoprecipitate Reduced”)
- Octaplas<sup>®</sup>, Pooled Plasma (Human), Solvent/Detergent Treated Solution for Intravenous Infusion (“Octaplas<sup>®</sup>”)

Commonly used names:

- Plasma (FFP, PF24, PF24RT24, Thawed Plasma)
- Cryo poor plasma
- Liquid Plasma
- Thawed Plasma

## I: FFP, PF24, PF24RT24 and Thawed Plasma

### Description

Plasma for transfusion is prepared by either centrifugation of whole blood or by apheresis. Multiple forms of plasma components are available based on differences in how the plasma is processed and stored following collection. Differences in the post collection processing or storage of plasma for the above or other plasma components cause variations in coagulation factor levels, fibrinolytic proteins, immunoglobulins, albumin, and other proteins. Despite differences in plasma protein (coagulation factor) levels, FFP, PF24, PF24RT24, and Thawed Plasma are generally used for the same indications with exceptions being noted in the Indications and Contraindications section. The plasma component name, volume, anticoagulant and expiration date are indicated on the label. Plasma is usually anticoagulated with citrate and units prepared from whole blood are approximately 200–250 mL while apheresis-derived units can contain 400–600 mL.

FFP is separated from whole blood and frozen at -18°C or colder within 6–8 hours of collection and contains physiological quantities of all coagulation factors, including Factors V and VIII.

PF24 is separated from whole blood and frozen at -18°C or colder within 24 hours of collection and differs from FFP by having lower Factor VIII and Protein C levels as well as variable levels of Factor V and other labile plasma proteins.

PF24RT24 is separated from whole blood and frozen at -18°C or colder within 24 hours of collection and differs from PF24 in being maintained at room temperature during transport and processing up to the time of freezing, that is, for a maximum of 24 hours. Levels of Factor V, Factor VIII and Protein S are reduced and other labile plasma proteins are variable in PF24RT24 as compared to FFP.

Thawed Plasma is derived from FFP, PF24, or PF24RT24 that has been thawed and maintained at 1 to 6°C for 24 hours. After the first 24 hours following thawing these plasma components are relabeled as Thawed Plasma which has a shelf life of up to

four days as Thawed Plasma if stored at 1 to 6°C. PF24, PF24RT24, and Thawed Plasma contain variably reduced levels of the labile factors V and VIII<sup>(3,4)</sup>.

## Indications and Contraindications<sup>(1,7,12,14-24)</sup>

### Indications:

- Active bleeding or risk of bleeding due to deficiency of multiple coagulation factors
- Urgent reversal of warfarin when 4 factor prothrombin complex concentrate is not available and cannot wait for Vitamin K to take effect
- Massive transfusion with coagulopathic bleeding
- Bleeding or prophylaxis of bleeding for a known single coagulation factor deficiency for which no concentrate is available
- Plasma Exchange for Thrombotic Thrombocytopenic Purpura (TTP). TTP is a medical emergency requiring immediate exchange plasma exchange. If plasma exchange is not immediately available, consider plasma transfusion as an emergency, secondary treatment until plasma exchange becomes available. Plasma Cryoprecipitate Reduced is sometimes used for the treatment of TTP.
- Rare specific plasma protein deficiencies for which no concentrate is available, e.g., fibronectin

### Exceptions:

- **PF24:** not to be used for replacement of labile coagulation factors such as Factor V, Factor VIII and Protein C
- **PF24RT24:** not to be used for replacement of labile coagulation factors such as Factor V, Factor VIII and Protein S
- **Thawed Plasma:** not to be used for the replacement in patients with isolated coagulation factor or isolated protein deficiencies in which other products with higher levels of the deficient factor or protein are available

### Contraindications:

- Increasing blood volume only or to increase albumin levels or for nutrition
- A coagulopathy that can be corrected by adjusting warfarin dose and/or administration of vitamin K.
- Normalizing abnormal coagulation screen results in the absence of bleeding.

## Selection and Preparation

Plasma for transfusion must be ABO-compatible with the recipient's red cells. Group A plasma is generally used for emergency transfusion until the patient's blood type is determined. Although Group AB Plasma is suitable for transfusion to patients of all blood types, it should be reserved for AB patients.

Frozen plasma must be thawed in an FDA-approved water bath or other FDA-approved device at 30 to 37°C. Although frozen plasma should be transfused immediately after thawing, it can be stored at 1–6°C for no longer than 24 hours. After the initial 24 hours, FFP, PF24 and PF24RT24 may be relabeled as Thawed Plasma and used as a source of stable coagulation factors for an additional 4 days.

## Dosing

Plasma dose is determined by patient weight 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<sup>(12-14)</sup>. This is usually achieved with the administration of 10–20 mL/kg patient weight, though more may be required depending on the clinical situation.

When used to correct isolated coagulation factor deficiencies for which no concentrated preparation is available (for example, Factors V and XI), dosing will depend on the pre-transfusion level of the factor, the desired post-transfusion level, the needed duration of higher levels, and the factor's half-life and volume of distribution<sup>(15)</sup>.

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 upper level of the normal range<sup>(15)</sup> or an INR of greater than 1.7<sup>(16)</sup> would warrant plasma transfusion. When such testing is not readily available, clinical evidence of bleeding may be used to direct transfusion decisions.



Thrombotic Thrombocytopenic Purpura (TTP) initially requires the exchange of 1–1.5 plasma volumes daily. In clinical practice, plasma exchange is often tapered after the first five days as disease activity declines, although this has not been studied prospectively<sup>(17)</sup>. (Please see the Cryoprecipitate chapter for plasma and blood volume calculations).

The efficacy of plasma is questionable in many clinical settings, but in general, plasma transfusion is more effective at higher INR values<sup>(12)</sup>.

Coagulation factor half-life should be considered when plasma is given prior to invasive procedures. For example, for a patient with Factor VII deficiency, the 4–6 hour in vivo half-life of Factor VII requires transfusion of plasma as close as possible to the time of the procedure to achieve hemostatic factor levels<sup>(10)</sup>.

*For side effects and hazards, please see the Appendices.*

## 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<sup>(12)</sup>.

Plasma used to treat TTP should result in an increasing platelet count associated with a decrease in serum lactate dehydrogenase<sup>(17)</sup>.

## II: Other Plasma Preparations: Liquid Plasma, Plasma Cryoprecipitate Reduced, Thawed Plasma Cryoprecipitate Reduced and Octaplas®

**Liquid Plasma** is plasma that has been separated from whole blood no later than five days after the expiration date of the corresponding whole blood unit, never frozen and stored at 1–6°C with a shelf life of 5 days after the expiration of the whole blood unit. Since coagulation factor levels in Liquid Plasma decline over time, the transfusion service should review the literature<sup>(6,6)</sup> to determine the maximum days of storage at which Liquid Plasma has the minimum coagulation factor levels needed to treat their patients. Liquid Plasma also contains viable lymphocytes with a theoretical but not substantive risk of Graft vs Host Disease. The only indication for Liquid Plasma is for the initial treatment of patients requiring massive transfusion because of life-threatening trauma or hemorrhage until other plasma components are not available such as at the trauma scene by first responders.

**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<sup>(6)</sup>. 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 or has reduced activity in thrombotic thrombocytopenic purpura (TTP). ADAMTS13 activity should remain stable for the duration of the shelf life of these thawed products<sup>(9)</sup>. Collection occurs in a closed system, so Plasma Cryoprecipitate Reduced can be used for up to five days post-thaw and relabeled as Thawed Plasma Cryoprecipitate Reduced<sup>(11)</sup>.

**Octaplas®** was approved by the FDA for use in the United States in January 2013. It is produced in pools of plasma from 630–1,520 donors, undergoes 1 µM filtration, solvent-detergent reagent treatment, and affinity column filtration to bind prion proteins. Units are supplied in ABO-specific 200 mL volumes<sup>(7)</sup>. Octaplas® has a 24 hour shelf life post-thaw if stored at 1°C to 6°C or 8 hours if stored at 20°C to 25°C<sup>(7)</sup>.

**Freeze Dried Plasma** is not approved by the FDA for use in the United States at this time. However, an Emergency Use Authorization (EUA) was granted to the Department of Defense by the FDA with the freeze dried plasma used by the military being obtained from a French manufacturer as it is not manufactured in the United States. Freeze Dried Plasma is prepared by lyophilization, that is, frozen plasma is placed into a vacuum which evaporates the plasma water resulting in a dried powder consisting of the remaining plasma components (coagulation factors and other proteins, etc.). The powder (freeze dried plasma) is reconstituted with sterile water at the time of use and has the advantages of not requiring storage in a freezer or refrigerator, quick preparation at the time of use and simplified transportation requirements making it ideal for use by first responders in the field or in an emergency room or trauma suite as well as in a general hospital setting.

## Utilization Guidelines<sup>(12, 18-44)</sup>

### Liver Disease

Plasma may be used to replace multiple coagulation factor deficiencies due to 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. Post-transfusion 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 INR-based doses of vitamin K and plasma or prothrombin complex concentrates as clinically warranted. Recent guidelines suggest that 4-factor prothrombin complex concentrates are preferable to plasma transfusion for situations requiring urgent reversal of warfarin<sup>(25-27)</sup>. Three-factor prothrombin complex concentrates have been proposed as an alternative without supporting randomized controlled trial data. These suggestions are based on limited evidence. When prothrombin complex concentrates are not immediately available, plasma transfusion may be necessary. As in 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 based on retrospective studies advocate using a high plasma-to-RBC ratio to improve survival. A recent randomized controlled trial comparing two high plasma-to-RBC ratios to each other but not to a laboratory driven model showed no difference in the mortality outcomes studied<sup>(32)</sup>. 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<sup>(33)</sup>. Further studies, including randomized controlled trials, are necessary to determine the risks or benefits of a high ratio strategy compared to a laboratory driven approach.

### Thrombotic Thrombocytopenic Purpura

If plasma exchange is not immediately available, simple transfusion of plasma might be an alternative until exchange can be initiated. With equivalent levels of ADAMTS13, plasma and Plasma Cryoprecipitate Reduced are equally efficacious in the treatment of TTP and newly diagnosed TTP<sup>(37)</sup>. If ADAMTS13 levels are 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 for which concentrates are not readily available are also treated with plasma and include:

- Prophylactic correction of a known factor deficiency for which specific concentrates are unavailable (would be 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 US).

### Pediatrics<sup>(42-44)</sup>

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 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.

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# Cryoprecipitated AHF



## General Information<sup>(1,2,3)</sup>

### Components

Approved names:

- Cryoprecipitated Antihemophilic Factor (AHF)
- Pooled Cryoprecipitated AHF

Commonly used names:

- Cryo
- Cryoprecipitate
- 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. The mean factor content of American Red Cross single units and pools (Red Cross pools contain 5 units) are: Factor VIII:C 136 and 555 IU, respectively, and fibrinogen 525 and 2450 mg, respectively. Cryoprecipitate produced from pathogen-reduced (PR) plasma was been granted a “Breakthrough Device Designation” in October 2018, but there is no FDA-approved PR-cryoprecipitate at the time of writing<sup>(4)</sup>.

### Selection and Preparation

Cryoprecipitate is considered to be an acellular blood component. Compatibility testing is unnecessary<sup>(5)</sup>; however, cryoprecipitate that is ABO-compatible with recipient red cells is common practice. Rh type need not be considered. CMV testing and leukoreduction are not required. Frozen cryoprecipitate is thawed in a protective plastic overwrap in a water bath at 30–37°C up to 15 minutes or in a microwave device approved by the FDA specifically for this use. 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<sup>(1,3)</sup>. 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 removal of as much material from the container as possible. Cryoprecipitate pooled prior to freezing requires no extra diluent.

There has been great interest in extending the post-thaw shelf life of cryoprecipitate<sup>(6,7)</sup>, and many reports have documented the stability of fibrinogen for 5 days<sup>(8)</sup> and even up to 35 days<sup>(9)</sup>. Stability of vWF has been demonstrated at 1 day<sup>(10)</sup> and 5 days<sup>(8)</sup>, and even up to 14 days<sup>(9)</sup>. As expected, FVIII activity dropped off dramatically in all conditions, but this was preserved somewhat with refrigeration<sup>(9)</sup>. PR-cryo has demonstrated the ability to correct dilutional coagulopathy in vitro<sup>(11)</sup>, but this product is not yet FDA-approved.

Mitigating the enthusiasm for possibly extending the expiration date of cryoprecipitate is the concern for possible bacterial contamination of products stored at room temperature. Post-thaw spiking experiments demonstrated negligible growth of inoculated bacteria at 4 hours post-thaw but showed marked increases in bacterial proliferation after 24 hours of room-temperature storage<sup>(12)</sup>. Early spiking of whole blood shows variable, but frequent, bacterial growth in manufactured cryoprecipitate at 5 days post-thaw, supporting the concern that even if only trace bacteria were present at collection, growth

can occur during prolonged storage<sup>(13)</sup>. Despite deliberate whole blood inoculation, some cryoprecipitate samples actually had negative cultures after 5 days of storage in this study, suggesting that some other attribute of post-collection manipulation, such as bacterial sedimentation during centrifugation prior to plasma manufacturing and freezing, may limit the appearance of clinically-relevant septic transfusion reactions after cryoprecipitate or plasma transfusion. Real-world assessments of cryoprecipitate sterility with prolonged storage have had mixed results. It is encouraging that two reports found no bacterial growth in cryoprecipitate (10 pools were negative after 1 day of refrigeration<sup>(10)</sup> and eight pools were negative at 35 days in another study (four refrigerated and four at room temperature)<sup>(9)</sup>. However, one of twenty pools in a longitudinally-sampled study did demonstrate *Staphylococcus epidermidis* after 5 days of ambient temperature storage<sup>(8)</sup>. Since each product was serially sampled in that report, the possibility of laboratory-associated contamination due to repeated product entry could not be excluded. PR-cryo is expected to have even less bacterial growth<sup>(11)</sup>.

## Dosing and Response

The minimum fibrinogen content per unit is 150 mg; however, most products contain considerably more. As for many blood products and pharmaceuticals, the first steps in determining the cryoprecipitate dose for fibrinogen replacement are the calculations of the patient's total blood volume and then the patient's plasma volume. There are two methods for determining the desired fibrinogen dose (Box 1). For dosing purposes, an increase in intravascular fibrinogen content between 200-250 mg/unit is typically estimated, as in Formula 1<sup>(14)</sup>. A dosing strategy that empirically accounts for the fact that fibrinogen has an extravascular distribution of about 30% is presented in Formula 2. When ROTEM data is utilized, dosing is usually standardized to two bags of 5 pools for adults.

## Dosing Cryoprecipitate

### ▪ Calculation of Total Blood Volume (TBV):

$$\text{Total Blood Volume (mL)} = \text{Patient's Weight (kg)} \times \text{Blood Volume Estimate/kg* (mL/kg)}$$

### ▪ \*Mean blood volume estimates<sup>(15,16)</sup>

- Average adult female: ~65 mL/kg
- Average adult male: 70 mL/kg
- Pre-term neonate: 80-105 mL/kg
- Term neonate: 90 mL/kg
- Neonate 1-6 months: 85 mL/kg
- Child, 6 months—12 years: 75 mL/kg
- Pregnancy: can increase 45%; estimate per kg depends on gestational age, multiple gestation, and pre-gravid weight<sup>(17-19)</sup>.

### ▪ Calculation of Plasma Volume (PV):

- Plasma Volume (mL) = Total Blood Volume (mL) × (1.0 – Hematocrit (%)) *Hematocrit needs to be expressed as a decimal.*

### ▪ Calculation of Fibrinogen Required (mg) and number of cryoprecipitate units: 2 methods:

#### - Formula 1 estimates intravascular distribution:

- Fibrinogen desired (mg) =
- PV (mL) × (desired fibrinogen – current fibrinogen (mg/dL)) × 0.01 (dL/mL)
- Estimate 250 mg fibrinogen average intravascular content per unit
- # units = Fibrinogen desired (mg) ÷ 250 mg/unit

#### - Formula 2 accounts empirically for extravascular fibrinogen:

- Fibrinogen desired (mg) =
- PV (mL) × (desired fibrinogen – current fibrinogen (mg/dL)) × 0.01 (dL/mL) ÷ 0.72<sup>20</sup>
- Use actual ARC average fibrinogen content of 525 mg per unit
- # units = Fibrinogen desired (mg) ÷ 525 mg/unit



- **Using ROTEM/FIBTEM data:**

- Adult dose (10 units or 2 pools of 5 units): FIBTEM A10 (or MCF) <sup>(21)</sup> <10mm <sup>(22)</sup> or <12 mm <sup>(23)</sup>

**For example, to increase fibrinogen from 50 to 100 mg/dL in an adult female (65 kg, 40% hematocrit):**

- 1.  $65 \text{ kg} \times 65 \text{ mL/kg} = 4,225 \text{ mL}$  blood volume
- 2.  $4,225 \text{ mL} \times (1.0 - 0.4) = 2,535 \text{ mL}$  plasma volume
- 3. Fibrinogen required =
- **Using Formula 1:**
- $(100 \text{ mg/dL} - 50 \text{ mg/dL}) \times 2,535 \text{ mL} \times 0.01 \text{ dL/mL} = 1267.5 \text{ mg}$  intravascular fibrinogen. Thus,  $1267.5 \text{ mg} \div 250 \text{ mg}$  average estimated intravascular fibrinogen rise per unit  $\approx 5$  units
- **Using Formula 2:**
- $(100 \text{ mg/dL} - 50 \text{ mg/dL}) \times 2,535 \text{ mL} \times 0.01 \text{ dL/mL} \div 0.72 = 1760.4 \text{ mg}$  total body fibrinogen. Thus,  $1760.4 \text{ mg} \div 525 \text{ mg}$  average unit content  $\approx 3.4$  units

Pre-transfusion and post-transfusion 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, so serial sampling would be warranted. The half-life is approximately 4 days in the absence of increased consumption such as in disseminated intravascular coagulation or major bleeding.

## General Information

### Indications and Contraindications

Cryoprecipitate is indicated for bleeding associated with fibrinogen deficiencies<sup>(24)</sup>. Routine use of cryoprecipitate as an alternative treatment for congenital fibrinogen deficiency, dysfibrinogenemia, Factor XIII deficiency, hemophilia A, or von Willebrand disease is not recommended and should be considered only when there is risk of loss of life or limb and the specific factor concentrate is not available<sup>(25)</sup>. Use of this component may be considered for uremic bleeding after other modalities have failed<sup>(26)</sup>.

*For side effects and hazards, please see the Appendices.*

### 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 patient's blood to artificial surfaces, hemodilution, hypothermia, and/or acidosis<sup>(27)</sup>. Established historical guidelines have recommended maintaining fibrinogen levels above a critical low level of 100 mg/dL in bleeding patients<sup>(28)</sup>, although this threshold was not based on clinical trials. More recent studies in obstetric, trauma, and cardiac surgery patients indicate that higher levels (150–200 mg/dL) <sup>(29-31)</sup> improve clot strength <sup>(30)</sup> and in vitro parameters, and may improve clinical outcomes<sup>(33)</sup>. FIBTEM data is also frequently used as a transfusion trigger for cryoprecipitate, and more frequently, for fibrinogen concentrate, dosing, since the real-time, intra-operative setting of this test are appealing for seriously bleeding patients<sup>(34)</sup>. Substituting alternative fibrinogen sources for cryoprecipitate in bleeding is an area of active investigation with promise in many clinical settings, and some clinical guidelines have favored fibrinogen concentrates over cryoprecipitate due to its ease of reconstitution and consistent dosing<sup>(35)</sup>. However, the unexpected finding of increased transfusion in patients randomized to receive fibrinogen concentrates compared to placebo<sup>(36,37)</sup> shows that further data on timing and impact on clinical outcomes are required<sup>(38)</sup>. Several clinical trials comparing timing and source of a fibrinogen source in cardiac surgery and trauma patients are ongoing and highly anticipated<sup>(38-42)</sup>.

### Fibrin Sealant

Although allogeneic cryoprecipitate had been used in the past as part of a hemostatic surgical adhesive, safer options are now available<sup>(43)</sup>. Several commercially produced, virus-inactivated, allogeneic sealants and autologous fibrin sealant systems are FDA-approved and are preferable to cryoprecipitate with respect to safety and efficacy for topical use<sup>(44-46)</sup>.

### Massive Transfusion

Transfusion for bleeding is often required after one or more blood volumes have been replaced, with rapid consumption of fibrinogen<sup>(47,48)</sup>. Algorithms employing early fibrinogen infusion have not been validated for efficacy or safety with cryoprecipitate,

but higher levels (150–200 mg/dL) may be beneficial in treating trauma, obstetric, and cardiac surgery patients<sup>(29-31,47,49-51)</sup> and are recommended by some international interdisciplinary groups<sup>(31)</sup>.

## 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<sup>(26,50)</sup>.

## 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<sup>(52)</sup>.

## Congenital Factor Deficiencies

### Congenital Fibrinogen Deficiency

In 2009, a human-derived, virus-inactivated fibrinogen concentrate was approved by the FDA and is now considered first-line treatment for congenital fibrinogen deficiency<sup>(25,51,53)</sup>. 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<sup>(52)</sup>. Fibrinogen supplementation for surgical prophylaxis is not always required if the patient is only moderately hypofibrinogenemic (>50 mg/dL) if the surgery is a low bleeding risk<sup>(54)</sup>. It is important to note that approximately equal proportions of patients with hypodysfibrinogenemia have a bleeding (41%) or thrombotic phenotype (43%); therefore, low levels of fibrinogen may also be associated with a dysfunctional fibrinogen that may in fact require anticoagulation<sup>(55)</sup>.

### 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. Recombinant vWF has been recently approved to control bleeding in adults with vWD<sup>(53,56)</sup>. DDAVP is the treatment of choice for type 1 vWD<sup>(57-59)</sup>.

### Factor XIII Deficiency

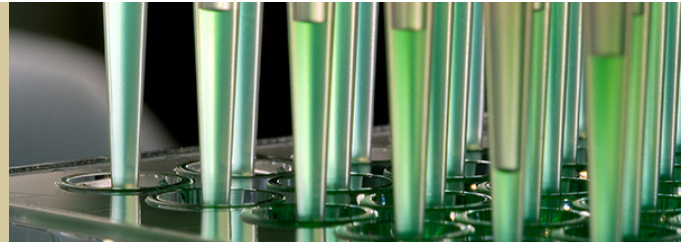
Deficiency of Factor XIII presents risk for severe bleeding, spontaneous abortion, and is associated with a 25–40% risk of spontaneous intracranial hemorrhage. Cryoprecipitate is not recommended and only used if virus-inactivated Factor XIII concentrates are not available<sup>(25)</sup>. Due to the high incidence of intracranial hemorrhage, newborns and some adults receive prophylactic dosing.

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## Testing Services



### Blood Testing (IRL, HLA, NNL, NML)

#### Overview

The Red Cross network of testing laboratories consists of Immunohematology Reference Laboratories (IRLs) in over 40 facilities, a National Reference Laboratory for Blood Group Serology (NRLBGS), a National Molecular Laboratory, multiple Human Leukocyte Antigen Laboratories (HLA), a National Neutrophil Laboratory and the National Reference Laboratory for Specialized Testing (NTLST).

These laboratories provide services to a wide range of patients coping with diseases such as cancer, sickle cell disease and other hematologic diagnoses resulting in anemia. They regularly support hospital-based sickle cell disease management programs, as part of efforts to enhance treatment plans and overall patient care.

### Red Blood Cell Serology

#### Red Cell Antibody Investigations

**Indication:** Red cell antibody investigations may become necessary during routine pretransfusion testing. The detection of most clinically significant red cell alloantibodies will ensure the patient is transfused with red cells or other blood components that provide normal red cell survival and do not cause an overt hemolytic transfusion reaction. Testing is performed as ordered by the hospital blood bank, pathologist, or the patient's physician

#### Description of commonly performed tests

**ABO/Rh:** Forward red cell typing and reverse serum grouping is used to determine an individual's ABO and D type, which may include the test for weak D. ABO/Rh resolution testing is performed when initial ABO/Rh test results are inconclusive. Resolution testing may include testing with multiple antisera, testing at reduced temperatures, enzyme treating red cells, performing adsorption/elution, red cell separations and/or molecular genotyping.

**DAT (Direct Antiglobulin Testing):** DAT testing is performed using Polyspecific Anti-IgG and Anti-C3b/C3d. For increased sensitivity, IgG testing can be performed in the IRL using the Gel system and other techniques to detect low levels of immunoglobulin on red cells. Detection of IgA, IgM and very low immunoglobulin levels of IgG can also be performed in some labs.

**Methodologies for Antibody Identification:** Antibody Identification may be performed using various methodologies which may include tube testing, Gel and/or solid phase according to testing protocols of the IRL. Multiple enhancement additives including low ionic strength solution, polyethylene glycol and bovine serum albumin are available and used as serologically dictated<sup>(1,2)</sup>.

- **Gel Test:** Gel testing is used for antibody identification and consists of plasma and red cells incubated in microtubes using Anti-IgG gel cards. Following incubation, cards are centrifuged and observed for agglutination.
- **Solid Phase:** A modified solid phase red cell adherence method is used. Plasma/serum and LISS are added to microwells immobilized with red cell membranes or red cells. Following incubation, the microwell strips are washed and IgG-coated indicator cells are added. The microwell strips are centrifuged and examined for red cell adherence.
- **Polyethylene Glycol:** Polyethylene Glycol is also used when performing antibody identification. This tube technique detects IgG reactive red cell antibodies<sup>(3)</sup>.
- **LISS (Low Ionic Strength Solution):** LISS is a potentiator used in tube testing to enhance antibody uptake to the red blood cells during sensitization<sup>(4)</sup>.

- **Ficin, Papain, EDTA Glycine-Acid, Dithiothreitol (DTT) and Chloroquine Diphosphate:** To facilitate antibody identification, red cells may be treated with any of the above reagents. Testing of the patient's plasma/serum against red cells that have been treated with chemicals may demonstrate the presence of additional antibodies directed against antigens not altered by the procedure. This may be helpful in the identification of those antibodies resistant to treatment. Treated cells are tested at the phase of optimal antibody reactivity. Chloroquine Diphosphate and EDTA Glycine-Acid are often used for removing cell bound IgG from red blood cells. This can be used prior to performing antigen typing in the presence of a positive DAT of patient's red blood cells who have not been transfused in the past 3-4 months. This treatment will also decrease anti-HLA (e.g. Bg) reactivity<sup>(5-7)</sup>.

**Test of Record Crossmatch:** Testing is performed to determine in-vitro serologic compatibility using recipient's serum/plasma and the donor's cells.

**Adsorptions:** Many types of adsorptions may be used for antibody identification including allogeneic, autologous, rabbit erythrocyte stroma and Human Platelet Concentrate (HPC).

- **Allogeneic Adsorption:** Allogeneic adsorption is indicated for recently transfused patients who demonstrate antibodies directed against all reagent red cells as well as their own. Red cells from donors with phenotypes that will allow identification of antibodies to common antigens are used as untreated or enzyme treated adsorbing cells. The patient plasma is adsorbed onto the cells, removing the autoantibody. The adsorbed plasma is tested for the presence of underlying alloantibody. This technique may also be used for separation of multiple antibodies. This technique is used to remove antibody directed against high prevalence antigens allowing for the identification of underlying antibodies to additional red cell antigens. Allogeneic adsorptions will not allow detection of alloantibodies directed against high prevalence antigens<sup>(8,9)</sup>.
- **Autologous Adsorption:** Autologous adsorption is the preferred method for removing autoantibody reactivity; however, it is only indicated for patients who have not been transfused within the last 3-4 months. Autologous adsorption can be facilitated by dissociating autoantibody by treatment of the red cells, uncovering antigen sites that can bind free autoantibody to remove it from the serum. The adsorbed plasma is then tested for the presence of underlying alloantibody. Since the patient's own cells are used for adsorption, exclusion of antibodies to high prevalence antigens can be performed<sup>(10-12)</sup>.
- **Evaluation of Cold Autoantibodies:** Various techniques are utilized by the IRL when evaluating samples with cold autoantibodies. Serological exclusions of clinically significant alloantibodies may be facilitated by cold autoadsorptions and/or adsorptions of the sample with Rabbit Erythrocyte Stroma (RESt)<sup>(13-15)</sup>.

**Cold Agglutinin Titration:** For cold-reactive autoantibodies, cold agglutinin titrations may be performed to determine pathologic cold agglutinin disease. Sample is separated and prepared for testing at 37°C. Titration of the sample is performed, and the resulting titer may assist in the diagnosis of cold agglutinin disease.

**Thermal Amplitude:** For cold-reactive antibodies, in-vitro thermal amplitude studies may be performed with serum to evaluate the reactivity of the antibody at different temperatures. The sample should be drawn and immediately separated at 37°C and used for thermal amplitude testing. Serially diluted serum is tested at 37°C, 22°C, 10°C and 4°C against a variety of cells to determine the thermal range of reactivity of the patient's antibody, antibody specificity and can be useful in diagnosis<sup>(16)</sup>.

**Elution:** The acid elution method is the most frequently used method for eluting antibody from red cells. The Freeze-Thaw (Lui) elution method and/or 56oC Heat Elution methods are frequently used for samples with a suspected ABO incompatibility or ABO discrepancy investigation<sup>(17,18)</sup>.

**Cell Separation:** Cell separation is performed to isolate autologous red cells from donor cells in a recently transfused patient. Separated autologous cells can be used for antigen typing and additional testing.

- **Hypotonic Wash for Cell Separation:** Red Cells with HgbA hemolyze in a hypotonic solution. Washing cells with hypotonic saline separates HgbS containing red cells from HgbA containing red cells by hemolyzing HgbA cells. This method is used to perform antigen typing in recently transfused patients with Sickle Cell Disease when testing by molecular methods cannot immediately be performed<sup>(19)</sup>.
- **Reticulocyte Separation:** In recently transfused patient samples, a reticulocyte separation may be performed using the microhematocrit centrifugation method for antigen typing needs. This allows separation of transfused red blood cells from the patient's very young red blood cells (reticulocytes). This method is used to perform antigen typing when testing by molecular methods cannot immediately be performed<sup>(20)</sup>.



**Antibody Titration and Scoring of Results:** Antibody titration is useful in prenatal studies and characterizing possible “HTLA-like” antibodies. The “score” of titration results is only reported on prenatal specimens. All prenatal titrations are performed using the standard 60-minute saline technique. The titer will be reported as the reciprocal of the last dilution displaying 1+ reactivity for prenatal titration studies and the last reactive dilution for studies involving “HTLA-like” antibodies.

**Drug Studies:** Drug studies can be performed to evaluate the serum to determine the presence of drug dependent immune antibodies against red cells and platelets.

**Neutralization:** Antibodies towards ABH, Lewis, anti-P1, I, Sda, Chido and Rodgers antigens can be inhibited by the soluble form of the antigens. Inhibition or neutralization can be used to confirm antibody specificity or allow identification of additional antibodies<sup>(21)</sup>.

**Polyagglutination Studies:** Lectin testing is useful for classification of polyagglutination<sup>(22)</sup>.

**IgG vs. IgM Determination:** Treatment of serum/plasma with sulfhydryl reagents (Dithiothreitol) is useful in differentiating IgM antibodies from IgG antibodies<sup>(23)</sup>.

**Fetal Maternal Hemorrhage Testing:** Kleihauer-Betke stain is a quantitative test that can be performed to determine the volume of fetal cells in the maternal circulation. The stain is used most often to determine the dosage of Rh immune globulin needed following a fetal-maternal bleed in an Rh (D) Negative woman who has delivered an Rh (D) Positive infant.

## Antigen Negative Blood Products

### Indication

For patients with special red blood cell antigen negative requirements. Immunohematology Reference Labs (IRLs) maintain an inventory of known antigen types to assist hospitals with antigen-negative blood needs. IRLs work through the American Rare Donor Program (ARDP) to locate and obtain rare units not available in inventory. By possessing the largest product inventory, the Red Cross is a major source for rare blood products. We provide coverage 24 hours a day, 7 days a week to ensure that all requests are received and addressed as quickly as possible.

### Description of commonly performed tests

**Antigen Typing:** Antigen testing is performed for patient and donor samples. An inventory of rare unlicensed antisera is maintained and used to perform typing when no commercial source exists. Molecular genotyping for common antigens can also be performed.

**Hemoglobin S Testing:** The IRL performs qualitative HgbS screening on donor units upon request.

### Products Offered

- Single and multiple antigen-negative RBC units
- RBC units negative for high and low prevalence antigens
- HgbS negative RBC units
- Rare frozen/deglycerolized red blood cells – 24-hour expiration date
- Access to the ADRP for rare RBC components including Rh allele matching for variant Rh antigens.

## American Rare Donor Program

### Description

The American Rare Donor Program (ARDP) was established over 20 years ago and exists to ensure that matching blood can be found for patients with rare blood needs. A person's blood type is considered rare if it is found in less than one in 1,000 people. The rarer a person's blood type, the more challenging the circumstances if that person suddenly needs matched blood for a transfusion. ARDP members consist of Red Cross and AABB-accredited Immunohematology Reference Laboratories (IRL). Blood units collected at ARDP member facilities are available to other ARDP member facilities upon request. In addition, non-ARDP member facilities with a transfusion request for rare blood units may access the ARDP by contacting a member facility, making the services of the ARDP available to all transfusion services and to all patients, both nationally and internationally.

## Molecular Testing for Red Cell Antigen Prediction

### Indications for Use

- For patients who have been recently transfused such that red cell phenotyping is not possible or reliable after red cell treatments such as EGA, reticulocyte separation or hypotonic wash<sup>(27)</sup>
- For patients with a positive direct antiglobulin test (DAT)
- For patients with warm autoantibody<sup>(40)</sup>
- For patients being treated with immunologic agents such as anti-CD38 or daratumumab<sup>(42)</sup>
- For patients with hemoglobinopathies such as sickle cell disease and thalassemia<sup>(34,39)</sup>
- For determining the red cell phenotype for an antigen for which antisera is unavailable or unreliable (such as V, VS, Jsa, Doa, Dob, Joa, Hy, hrB, hrS)
- For patients with red cell typing discrepancies including ABO, RH, MNS, FY, JK, KEL, LU
- For patients who has produced an antibody to an antigen that they express where an antigen variant may be suspected (eg., Rh variant antigens in patients of African descent)
- For determining zygosity of red cell antigens in partners of women at risk for hemolytic disease of the fetus and newborn (HDFN)
- For differentiating U- from U+VAR
- For differentiating Lu(a-b-) from In(Lu)

### Red Blood Cell Genotyping Panel

- Currently, there are two FDA-approved RBC genotyping panels for human erythrocyte antigens (HEA) and several “research use only” panels. These panels are based on single nucleotide variants (SNVs) that are known to create, destroy or alter antigen status. These low-resolution test methods do not include all known variants and lack most of the null alleles that silence antigen expression. The extended antigen phenotype prediction is useful in patients on chronic transfusion regimens. In alloimmunized patients, it can be used to assess the additional alloimmunization risk.
  - The HEA panel includes markers that differentiate U- from U+VAR, with the information used to select U- or U+VAR blood products in patients with anti-U or -U-like antibodies.
  - The HEA panel includes markers to determine if a serologic Fy(b-) status is due to lack of FY\*B allele or silencing of the FY\*B allele due to presence of single nucleotide variant in a GATA-box in the gene promoter. Patients whose red cells are Fy(b-) due to this promoter variant are not at risk of anti-Fyb but anti-Fy3 has been reported<sup>(28,29)</sup>.
  - The HEA panel includes RHCE markers that, if detected, suggest that the sample may carry an RHD gene expressing a partial C antigen. Additional RH genotyping may be necessary to definitively demonstrate this. This information can aid in determining the risk of alloanti-C in patients who type C+.

**RHD Genotyping** is used to identify RHD variant alleles and predict the D antigen phenotype. RHD genotyping is performed using a commercially-available “Research Use Only” genotyping panel that can detect many weak, Del and partial alleles including weak D types 1, 2 and 3. RHD genotyping may also include performance of one or more lab-developed tests to rule out weak or partial alleles not interrogated on the commercial panel.

- RBCs expressing either weak or partial D antigen expression can demonstrate a serologic weak D phenotype<sup>(32)</sup>.
- Resolution of a serologic weak phenotype is especially important in pregnant women and women of child-bearing age, as the decision regarding Rhlg prophylaxis is informed by the RHD variant type. Specifically, individuals who are homozygous or hemizygous for weak D types 1, 2 and 3 are not at risk of D alloimmunization<sup>(32,33)</sup>.
- Weak or partial RhD antigen expression can result in typing discrepancies, either between test methods, reagents, labs or between a current and historic type<sup>(35)</sup>.
- There are hundreds of RHD variant alleles<sup>(38)</sup>. RhD variant antigens can have weakened and/or altered antigen expression and may express a partial phenotype defined as an antigen missing one or more epitopes recognized by monoclonal anti-D reagents. RhD variants can also gain low prevalence antigens by expressing neopeptides.
- RHD variants are found in all ethnic groups but are most common in individuals of African descent<sup>(37)</sup>.
- Patients who type D+ with anti-D that shows properties of an alloantibody may benefit from RHD genotyping

**RHCE genotyping** for predicting C, c, E, e, V, VS, hrB, hrS can be beneficial in some scenarios, to determine if the patient expresses variant Rh antigens and determine the specific alloimmunization risks. RH characterization includes use of RHD and RHCE commercially available “Research Use Only” genotyping panels and may also include performance of one or more lab-developed tests to rule out variant alleles not interrogated on these commercial panels.

- Rh alloimmunized patients who express the antigen for which an antibody has been detected (C+ with anti-C, e+ with anti-e) may benefit from genotyping.
- Patients of African descent who are or will be on a chronic transfusion regimen, such as those with hemoglobinopathies including sickle cell disease.
- Patients who are found to have D variants may be at risk of expressing altered RHCE antigens and visa versa, since RHD and RHCE alleles are often co-inherited and variant RH haplotypes are not uncommon in individuals of African descent.
- Patients of in whom an antibody to a high prevalence antigen in the Rh system, such as hrB, hrS, HrB is suspected. In a scenario in which the patient has made such an antibody and identification of compatible blood is challenging, RH allele matching through the American Rare Donor Program can be considered.
- Patients who are found to be compound heterozygotes for single nucleotide variants in RHCE and who are on chronic transfusion regimens and/or are alloimmunized can benefit from testing that can determine the phase of the variants. This testing can involve cDNA analysis and cloning into plasmid vectors followed by Sanger sequencing

**RHD zygosity** in the case of women at risk for hemolytic disease of the fetus and newborn (HDFN) can aid in determining the level of monitoring of a pregnancy. Testing involves several lab-developed tests designed to detect inactive forms of the RHD gene including hybrid Rhesus box and RHD pseudogene as well as RHD variant alleles expressing a partial C and not a D antigen.

- Zygosity testing can be performed on the alleged partner of the alloimmunized woman, or fetal material can be obtained from amniocentesis
- Noninvasive prenatal diagnostic testing for RHD using circulating cell-free fetal DNA (ccffDNA) from the plasma of a pregnant woman is used in some European countries to screen RhD negative women to determine their candidacy for Rh immunoprophylaxis. Currently, ccffDNA testing is not routinely performed in the US.
- Though serologic testing of the male partner can be done for other antigens for which non-functional alleles are not common (eg. K), RBC genotyping using an HEA panel can also be used.

**ABO Genotyping** can be a useful tool for ABO typing discrepancies<sup>(31)</sup> and to determine if a candidate kidney donor carries an A2 subgroup such that the organ can be transplanted to a group B recipient for whom insufficient ABO matched organs are available

- Determination of ABO common alleles (A1, A2, B, O1, O2) can be performed using a commercial “research use only” genotyping panel or lab-developed test. This low-resolution testing cannot rule out the presence of rare subgroups<sup>(30)</sup>.
- High resolution testing using Sanger sequencing can be performed when ABO subgroup (other than A2) is suspected. ABO variant alleles (eg., B(A), Ax, Aw, Am, cisAB) can be identified using this technique<sup>(30)</sup>.

**Non-RH, non-ABO Genotyping** using lab-developed tests that interrogate variants other than those on commercial platforms can be a useful in specific scenarios. This testing can involve assays to genotype specific single nucleotide variants associated with weak or partial antigens or can involve high resolution assays designed to interrogate all or specific parts of a gene or gene transcript to rule out rare or novel variants.

- A patient who types Jk(a+) with anti-Jka may carry a variant that puts them at risk of alloimmunization.
- A patient who types M-N- or M-N-S-s- may carry a gene deletion associated with a rare phenotype (En(a-) or MkMk]. The deletion can be demonstrated by using PCR amplification of sections of the GYPA and/or GYPB genes.
- A patient who types Lu(a-b-) may benefit from genotyping of the KLF1 gene to rule out the In(Lu) phenotype. Patients with the In(Lu) phenotype express Lutheran antigens (and AnWj and P1 antigens) weakly and do not typically make alloantibodies to Lutheran system antibodies.

## **Molecular Testing for Human Platelet Antigen (HPA) Prediction**

### **Indications for Use**

- In support of differential diagnosis of Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT). Diagnosis is confirmed if HPA antibody is demonstrating in the maternal serum and there is incompatibility for the antigen on the paternal platelet<sup>(24-26)</sup>.

- In support of differential diagnosis of platelet refractoriness due to anti-HPA antibodies. Platelet refractoriness due to immune causes can be due to anti-HLA, ABO or HPA antibodies.

## Description

- Currently, there are several commercial genotyping assays that test for a panel of HPA antigens, including the antigens associated with FNAIT and platelet refractoriness, including HPA-1a, -2b, -3b, -5b, -15b
- The predicted phenotype of the patient can be used in combination with platelet serologic testing, when available, to determine if selected HPA-antigen negative platelet products would benefit the patient
- HPA-1a, also known as PLA-1, is expressed on the GPIIb molecule. Antibodies to HPA-1a are responsible for the majority of FNAIT cases. Only 12% of HPA-1a negative mothers of HPA-1a positive fetuses make anti-HPA-1a and 90 of these mothers also carry the HLA DRB3\*01:01 <sup>(19)</sup>.

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# Therapeutic Apheresis



## Introduction

The term therapeutic apheresis describes multiple therapeutic procedures: therapeutic plasma exchange (TPE), red cell exchange (RBC exchange), extracorporeal photopheresis (ECP), leukocytapheresis, thrombocytapheresis, hematopoietic stem cell collection (HSCT), and lipoprotein apheresis (LA). There are other TA procedures including immunoadsorption (A), double filtration plasmapheresis (DFPPP), adsorptive cytapheresis, and rheopheresis. In the United States, the majority of TA machines separate whole blood mostly through filtration or centrifugation. Filtration is based on the physical size of the whole blood elements, while centrifugation is based on the specific gravity of cellular elements. Processing of whole blood can be either discontinuous or continuous. A discontinuous cycle involves certain volumes of blood being pulled into the machine, processed or manipulated, returned, and then repeated until the desired volume is accomplished<sup>(1)</sup>.

## Therapeutic Apheresis Technology

The continuous TA cycle places the patient in “circuit” with the apheresis machine until a certain predetermined volume is processed with the remainder of the components returned to the patient<sup>(1)</sup>. So-called membrane devices adjust transmembrane pressures to achieve appropriate blood separation, while centrifugal devices use a combination of centrifugal acceleration and centrifugal dwell time to separate<sup>(1,2)</sup>. Newer machines adjust these elements automatically using computer-based algorithms; older machines required operator adjustment<sup>(1)</sup>. Newer apheresis instruments also have smaller extracorporeal volumes, allow for anticoagulation flow rate adjustments as well as inlet flow rate adjustments, and possess alarms to detect clotting/pressure issues/air issues all of which make TA modalities more clinically palatable<sup>(4)</sup> for patients. This has also assisted in making many pediatric TA procedures possible<sup>(1)</sup>.

## Therapeutic Apheresis: Effectiveness

For a TA procedure to be effective, it must be able to remove or manipulate a substance that resides in the intravascular space. Removal kinetics of therapeutic plasma exchange (TPE), i.e., the efficiency of pathologic substance removal, depends on several elements (figure 1)<sup>(3-5)</sup>.

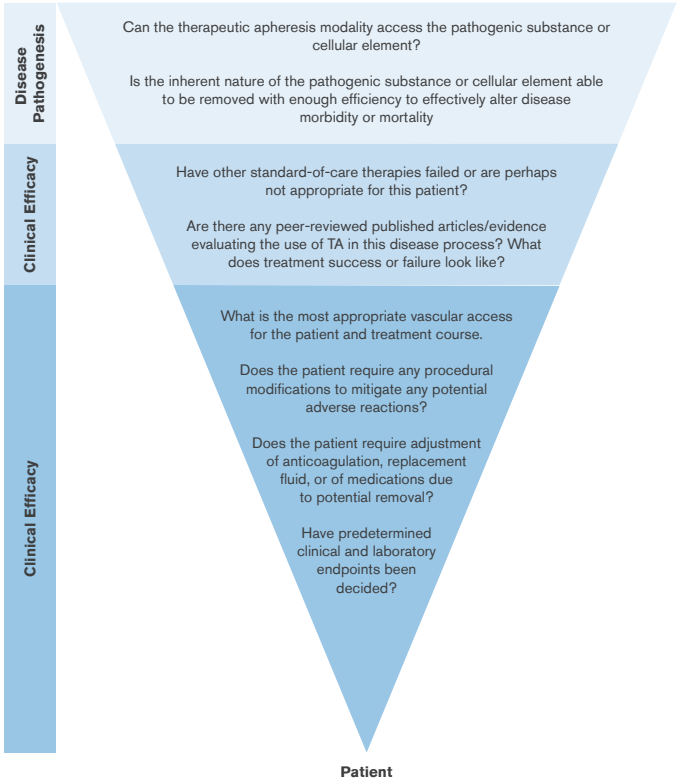


Figure 1. Therapeutic Apheresis Decision Tree



The first is the distribution of the substance between the extravascular space and intravascular space. For simplicity, many TPE models show the intravascular plasma volume as a closed system, when, in reality, there is fluctuation<sup>(6)</sup>. More specifically, the pathologic substance must have a concentration within the intravascular space that can be sufficiently removed to aid in resolution of disease morbidity<sup>(3)</sup>. For example, red blood cells are only present intravascularly: their removal can be very efficient. However, many proteins including immunoglobulins can diffuse between the intravascular and extravascular space depending on their size: IgG is 55% extravascular, IgA 58% extravascular, and IgM 22% extravascular<sup>(7)</sup>. Substances like bilirubin and ammonia diffuse continuously between the two spaces<sup>(7)</sup>. Moreover, the synthetic and catabolic rates of the pathologic substance need to be considered when planning a TA procedure. The catabolic rate of the pathogenic substance or cell cannot be too rapid because removal by a TA procedure will not be clinically meaningful<sup>(3)</sup>. Similarly, a substance with a high synthetic rate might not be sufficiently removed to provide benefit<sup>(3)</sup>. Substances that are effectively removed by TA are predominately intravascular (~50%), have a long half-life, and are slowly resynthesized<sup>(3-5)</sup>.

## **Apheresis Indications**

In an effort to collate clinical information on the use of TA in medicine, the American Society of Apheresis (ASFA) publishes clinical guidelines categorizing the indications for apheresis in 157 disease states<sup>(8)</sup>. The ASFA writing committee updates the guidelines on a three-year cycle and does a thorough evaluation of the peer-reviewed published literature using an international group of apheresis practitioners. They have categorized the use of TA in each of the disease states according to a 4-point scale. Category I are disorders for which apheresis is accepted as a first-line therapy whereas Category IV are disorders where the published evidence demonstrates lack of efficacy of TA and sometimes even harm<sup>(8)</sup>. The ASFA guidelines also assign a grade to the supporting literature so that the user may be fully aware of the strength of the studies that underpin the categorical designation<sup>(8)</sup>. While an excellent evidence-based tool to inform apheresis treatment decisions, the ASFA guidelines are only as good as the published evidence to support the indications and are not able to represent all the diseases for which a TA procedure may be clinically useful<sup>(5)</sup>. Each TA modality described forthwith considers the ASFA-specific indications.

## **Apheresis Procedural Considerations (lab eval, vascular access, procedural hemostasis)**

Vascular access is often the rate limiting factor for TA procedures. Peripheral access via antecubital veins should be attempted first whenever possible but one must consider the acuity of the clinical situation, the duration of TA required, and individual patient characteristics when determining optimal vascular access. Should the patient be well-hydrated, a single planned procedure (in an older child, teenage, or adult), peripheral access via two large caliber intravenous (IV) lines may be adequate<sup>(9,10)</sup>. However, for emergent procedures when temporary (i.e. less than a week of therapy) access is required then central venous access may be indicated in the form of rigid polyethylene or Teflon catheters or even semi-rigid polyurethane catheters<sup>(9,10)</sup>.

For longer duration of weeks-months, a tunneled line should be considered<sup>(9)</sup>. Permanent catheters are tunneled under the skin prior to insertion into the vein, and an area of rough material (the cuff) serves as a barrier to infection and anchors the catheter in place subcutaneously once healing has occurred<sup>(10)</sup>. The cuff allows the skin and subcutaneous tissue to grow around and onto it effectively keeping the line securely in place. Whenever possible, consider placement of a permanent catheter when the length of anticipated therapy is greater than 2 weeks<sup>(11)</sup>. It is always important to remember that the Center Centers for Disease Control and Prevention (CDC) and Joint Commission (JC) guidelines advise choosing a catheter with the minimum number of lumens or ports necessary to manage the patient<sup>(12,13)</sup>.

For long term use over months to years, an implanted port (available in double and single lumen options) should be considered. The port is sutured into a functional pocket created in the subcutaneous tissue, usually in the area of the chest, and accessed via puncture with a non-coring needle into the self-sealing septum. Implanted ports are useful when long-term, intermittent therapy is planned for several months to years. Implanted ports have the following advantages over external catheters: they have lower rates of infection, do not require home care, have less negative impact on body image, and allow children to participate in most activities<sup>(11)</sup>. An implantable device has been FDA approved for use when long term apheresis access is vital<sup>(12)</sup>. It is a single lumen port that is able to be accessed long-term and has shown favorable flow rates up to 150 mL/min for apheresis including TPE<sup>(12,13)</sup>. Of note, the recently published evidence supporting its use has not included pediatric patients<sup>(12,13)</sup>.

All laboratory testing samples should be drawn prior to the procedure. This is especially important when blood donor products are used, such as with TPE and erythrocytapheresis for the treatment of thrombotic thrombocytopenia purpura (TTP) and sickle cell disease, respectively. In these situations, pre-procedure testing of the patient's blood reflects baseline clinical parameters; while blood samples drawn during and post procedure evaluate therapeutic apheresis response.

Anticoagulation is important to prevent clotting as the blood flows through the extracorporeal circuit. The two anticoagulants used are either citrate or heparin, with the former preferred for its safety and effectiveness profile. Citrate is generally administered as an Acid Citrate Dextrose – A, ACD-A, formulation with a pharmaceutical effect that binds calcium, a necessary element to blood clotting. There are certain patient conditions which are susceptible to citrate toxicity, a form of systemic hypocalcemia. For instance, in pediatric patients where liver development is immature and persons who display liver dysfunction the citrate may not metabolize the citrate sufficiently. Alternatively, patient's with electrolyte imbalance including low ionized calcium and magnesium levels may also increase the risk for citrate toxicity reactions<sup>(14)</sup>.

### **Apheresis Procedural Adverse Events (AEs)**

Therapeutic apheresis is not without risk, with published reports ranging from 4.3% to 50%<sup>(15-19)</sup>. Many factors can lead to apheresis related complications including the underlying patient's condition, the number of procedures performed, the type of replacement fluid and anticoagulant selected, as well as the kind of venous access used. AEs typically are mild to moderate and include hypocalcemia, hypovolemia, and allergic reactions due to anticoagulant and blood product exposures<sup>(15-19)</sup>. Rarely are more severe AEs reported but when they do occur they are associated with cardiac, neurologic, and infectious type complications, with even fewer cases resulting in death.

### **Therapeutic Plasma Exchange (TPE)**

TPE is a treatment that removes large volumes of patient plasma while replacing it with a substitute<sup>(20)</sup>. The mechanism of action of TPE is removal of pathologic antibodies and substances (e.g., immune complexes, inhibitors, cytokines, toxins) present in the intravascular space. For removal of pathologic substances, the equilibrium of that substance in the intravascular space is dependent upon the rate of synthesis, catabolism, and diffusion between intravascular and extravascular spaces<sup>(1)</sup>. When using donor plasma as the replacement fluid, TPE can serve a dual purpose by also replacing protein or coagulation factor deficiencies<sup>(6)</sup>. The operator of the apheresis device can calculate the patient's plasma volume via the Nadler equation, which can easily be achieved by inputting the patient's height, weight, age, and hematocrit into the apheresis device's computer system<sup>(21)</sup>. The most efficient procedure occurs with 1.0-1.5 plasma volumes exchange, as treating larger volumes is less effective in removing the target pathologic substance but does prolong the procedure time, increasing the AE rate from exposure to more anticoagulant and replacement fluid<sup>(6,20)</sup>.

The most common replacement fluid for TPE is 5% albumin. Saline can be used but only as a minor component (80% albumin, 20% saline) as it is associated with a higher rate of hypovolemic reactions<sup>(4,5)</sup>. Plasma replacement is indicated for the treatment of thrombotic thrombocytopenic purpura (TPP) as it provides not only antibody removal but also an enzyme replacement<sup>(9)</sup>. In conditions with underlying coagulopathies, such as liver disease, active bleeding, or 12-24 hours pre- or post-invasive procedure, plasma may be used in conjunction with 5% albumin, but replacing the volume of 5% albumin in the latter half of the procedure to ensure the patient receives the donor coagulation factors<sup>(5)</sup>. Serial TPE does deplete coagulation factors, the most notable being fibrinogen. It is recommended that replacement of fibrinogen (<100-120 mg/dL) with cryoprecipitate prior to TPE or incorporating plasma as part of the terminal replacement solution during the procedure<sup>(5,20)</sup>.

### **Cytapheresis**

Cytapheresis is the collection of cellular elements such as red blood cells (red blood cell exchange, RBC exchange, erythrocytapheresis), white blood cells (leukapheresis), or platelets (thrombocytapheresis) and can be used in both the patient and healthy blood donor population. This section will mainly focus on clinical implications for the patient population.

### **Red Cell Exchange/Erythrocytapheresis**

Red blood cell exchange is the removal of a portion of the patient's red cell mass with replacement by donor RBCs, saline, and/or albumin. As with TPE, use of the Nadler's equation will assist with calculating the volume of replacement fluid to be used, including the number of RBC units. Consideration should be made to the time required for RBC units to be typed and crossmatched and the potential complexity of testing, if the patient is alloimmunized. In these situations, alternative measures to support the patient (i.e. simple transfusion of a few units) may be required while awaiting this preparation time<sup>(21,22)</sup>.

RBC exchange is used to remove either defective or infected RBCs, as in the case of sickle cell disease and babesiosis respectively. This therapy most often benefits patients with sickle cell disease for the acute treatment and chronic preventive management of stroke as well as recurrent painful sickle cell crises. This is done by targeting a reduction in the percentage of Hb S to <30%<sup>(8,23,24,25)</sup>. Use of this procedure can help increase hemoglobin oxygen saturation levels by 1-6%, thus acutely enhancing oxygenation to the tissues while also reducing blood viscosity induced by the sickled cells<sup>(8,24)</sup>. Another benefit, particularly for patients who are dependent on long term red cell transfusions, is the reduction of iron overload<sup>(26)</sup>.

For the treatment of infected RBCs, as in babesiosis or malaria parasitemia with levels greater than 10% or those with significant co-morbidities, RBC exchange can rapidly decrease the parasitemia burden. Therapy is normally discontinued once the parasitemia burden reaches less than 5%<sup>(8)</sup>.

## Thrombocytapheresis

In the patient population, thrombocytapheresis is mostly used in cases of pathogenic rather than reactive or secondary thrombocytosis (circulating platelet count  $\geq 450 \times 10^9/L$ )<sup>(8)</sup>. In pathogenic or primary thrombocytosis, the platelets do not function normally putting the patient at increased risk of thrombotic as well as hemorrhagic events<sup>(8)</sup>. Primary thrombocytosis includes myeloproliferative neoplasms such as essential thrombocythemia (ET). ET puts the patient at risk for not only arterial or venous thromboembolic events, but can also lead to bleeding due to acquired von Willebrand syndrome when platelet counts are greater than  $1,000 \times 10^9/L$ <sup>(27)</sup>.

Thrombocytapheresis removes the excessive circulating platelets to help treat and prevent acute thrombotic symptoms, as well as enhance effectiveness of prescribed chemotherapy regimen. Prompt and appropriate pharmaceutical cyto-reduction is necessary to prevent platelet rebound following the procedure<sup>(8,28,29)</sup>. Due to the thrombotic nature of this disease, it is recommended to increase the amount of anticoagulant in the circuit and consider whole blood to anticoagulant ratios of 1:6-1:12 while typically processing 1.5 to 2.0 blood volumes. Heparin should be avoided to prevent platelet clumping in the apheresis circuit<sup>(8)</sup>. A single procedure can lower the platelet count by approximately 30 to 60%, but the patient should be carefully monitored for a rebound<sup>(8,29)</sup>.

## Leukocytapheresis (reduction and stem cell collection)

Similar to platelets, white blood cells (WBCs) may become pathologic and increase in number. Hyperleukocytosis as seen with acute myelogenous (AML) or lymphoblastic leukemia (ALL) is typically defined as a WBC of  $50 \times 10^9/L$  to  $>100,000 \times 10^9/L$ <sup>(8)</sup>. It has an incidence of 10-20% in AML and 10-30% in ALL<sup>(30)</sup>. Leukostasis, however, is a medical emergency characterized by a high blast count with signs and symptoms of decreased tissue perfusion. This is caused through obstruction of the microvasculature with clinical presentation including respiratory and/or neurologic distress. Symptoms of leukostasis can occur when the WBC count exceeds  $>100,000 \times 10^9/L$  in the case of AML patients,  $>400,000 \times 10^9/L$  for those diagnosed with ALL<sup>(8,31)</sup>. The smaller, less deformable and more mature leukocytes of ALL are less likely to cause leukostasis than the larger undifferentiated myeloid blasts of AML, which are also known to secrete larger quantity of cytokine and therefore propagating the inflammatory state<sup>(8)</sup>.

Initial therapy for leukostasis calls for stabilization of the patient while rapidly decreasing the WBC. This involves cyto-reduction with initiation of induction chemotherapy and concomitant administration of tumor lysis syndrome prophylaxis. For patients with leukostasis who are not able to undergo induction chemotherapy to rapidly decrease the WBC (i.e., have renal insufficiency), hydroxyurea with or without leukocytapheresis is recommended. A single leukocytapheresis procedure can decrease WBC by 30-60% and generally involves processing 1.5-2.0 patient blood volumes. However, there is conflicting data whether leukocytapheresis helps decrease early mortality rates<sup>(32)</sup>. A retrospective review by Giles et al. reviewed 146 patients with hyperleukocytic AML<sup>(33)</sup>. Seventy-one underwent leukocytapheresis and had reduced 2-week mortality compared to those who did not but they had no improved long-term or overall survival<sup>(33)</sup>. Oberoi et al.'s 2015 meta-analysis in patients with AML and WBC  $>100 \times 10^9/L$  demonstrated that leukocytapheresis did not impact early mortality<sup>(34)</sup>. More recently a propensity score-matched study also showed leukocytapheresis had no positive influence on early mortality ( $<2$  weeks) or on early complications in patients with either AML or ALL<sup>(35)</sup>.

While these studies are important, they are predominately retrospective in nature and thus have inherent limitations. Leukocytapheresis might have a role in patients suffering from leukostasis from a blast crisis though this procedure should not delay initiation of disease-modifying chemotherapy<sup>(8)</sup>. Additional prospective studies are needed to elucidate the appropriate role of leukocytapheresis in these challenging cases.

## Specialty Apheresis

### Lipoprotein Apheresis

Lipoprotein apheresis involves the removal of lipoprotein particles from the blood with return of the "lipoprotein-reduced" whole blood back to the patient. This can occur in several different ways including double filtration plasmapheresis (DFPP), heparin extracorporeal low-density lipoprotein (HELP) apheresis, polyclonal-sheep-anti-apoB-immunoabsorption, dextran-sulfate

plasma adsorption, dextran-sulfate whole blood adsorption, and polyacrylate whole blood adsorption. These selective procedures have the advantage over non-selective like TPE in that other important plasma components like cardioprotective high-density lipoprotein are not removed<sup>(36)</sup>.

The methods used in the US are a HELP-system and a dextran-sulfate plasma adsorption. In the HELP-apheresis system, the patient's whole blood is passed through a plasma separator and lipoproteins (low density lipoprotein, lipoprotein(a), and fibrinogen) are selectively precipitated with fibrinogen and heparin to form insoluble precipitates<sup>(37)</sup>. The precipitate is removed from patient plasma by a polycarbonate membrane, while the heparin is removed by a heparin adsorber<sup>(37)</sup>. The "lipoprotein decreased" plasma is then returned to the patient. A more commonly used system is low-density lipoprotein (LDL) apheresis. LDL-apheresis uses heparin as an anticoagulant and isolates plasma from whole blood via a plasma separator. Plasma is then run through a dextran sulfate-cellulose column. The dextran sulfate has a negative charge and structure similar to the LDL-receptor in the liver and thus binds lipoproteins (LDL, lipoprotein(a), and very-low density lipoprotein<sup>(37)</sup>). The "lipoprotein decreased" plasma is then returned to the patient.

Lipoprotein apheresis is used in a variety of clinical settings but has found the most utility treating patients who have familial hypercholesterolemia (FH). FH is an autosomal dominant disorder caused by mutations most commonly in the LDL receptor gene as well as proprotein convertase subtilisin kexin 9 and apoprotein B genes. Heterozygous FH affects approximately 1 in 200 to 300 individuals; homozygous FH is rarer only affecting 1:300,000 to 1:400,000. FH is characterized by elevated LDL levels, xanthomas, and a propensity to early onset atherosclerotic cardiovascular disease. Diet modification and statin therapy with or without ezetimibe is helpful in patients heterozygous for FH<sup>(38)</sup>. FH patients are also treated with statins, ezetimibe, a PCSK9 inhibitor, or both<sup>(39)</sup>. If these methods fail alternative medical therapies may be considered for lipoprotein apheresis. Long-term lipoprotein apheresis combined with LDL-lowering drugs can result in stabilization and regression of coronary atherosclerosis<sup>(40,41)</sup>.

## Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunotherapy wherein peripheral lymphocytes are collected by centrifugal apheresis, incubated with 8-methoxypsoralen (psoralen), then irradiated with ultraviolet light, and reinfused. It differs from the previously described therapies in that nothing is exchanged or reduced. ECP processes approximately 1.5L of the patient's total blood volume (TBV). Once collected, psoralen is injected extracorporally into the bag and the mixture is sent through a UV-A light source. One mode of action of ECP was attributed to crosslinking of DNA pyrimidine bases in both circulating and/or malignant T lymphocytes resulting in their undergoing apoptotic cell death<sup>(42)</sup>. This does not help to explain the totality of the anti-tumor effect seen in cutaneous T-cell lymphoma. Another potential mechanism addresses the increase in major histocompatibility complex class I expression after ECP activates cytotoxic CD+8 T cells that results in the elimination of malignant T-cell clones<sup>(43,44)</sup>.

ECP was initially developed to help treat patients with cutaneous T-cell lymphoma (CTCL, mycosis fungoides) by Dr. Edelson and colleagues in 1987 for the treatment of Sézary syndrome, an aggressive form of advanced cutaneous T cell lymphoma (CTCL)<sup>(45)</sup>; this is now an ASFA category I<sup>(6)</sup>. ECP is also for a treatment for patients with acute and/or chronic skin GVHD (ASFA category II) and for lung and cardiac transplant rejection (ASFA category II)<sup>(8,46)</sup>. Its use is expanding into the treatment of select autoimmune diseases such as pemphigus vulgaris, scleroderma, inflammatory bowel disease and nephrogenic systemic fibrosis (ASFA category III)<sup>(8)</sup>.

## Summary

Therapeutic apheresis has evolved greatly over the past 50 years with more to come. It is an important therapeutic option in a variety of clinical settings ranging from hematology to solid-organ transplant. TA ranges in utilization as an emergent procedure (e.g. TPE in the treatment of TTP) to chronic maintenance treatment (e.g. lipoprotein apheresis in homozygous FH). When making clinical decisions concerning the use of TA, providers are encouraged to review the most updated version of the evidence-based apheresis guidelines. Other excellent resources include national and international societal guidelines. TA procedures are relatively safe, but they are not without risk and apheresis operators and providers should be experienced practitioners. As with any procedure, the risks and benefits must be considered.

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# Blood Component Modification <sup>(1, 2, 3, 4)</sup>



## 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 the white blood cell content of cellular blood components is reduced. 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 bedside (post-storage)<sup>(3)</sup>. Prestorage leukocyte reduction is preferable to post-storage as it facilitates appropriate quality control testing and removes leukocytes prior to the release of cytokines, cellular debris, and intracellular microorganisms. Leukoreduction may also reduce erythrocyte storage-induced damage, transfusion reactions and the risk of infection<sup>(6)</sup>. It may also reduce HLA alloimmunization. Blood products that are customarily leukoreduced include red blood cells (RBCs), apheresis platelets and 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 a unit of RBCs, apheresis platelets or prestorage-pooled WBD platelets, must have a final white blood cell count of  $< 5 \times 10^6$ . <sup>(3)</sup> In order for pooled WBD platelets to meet this criterion, each single WBD platelet unit must have a residual leukocyte count of  $< 8.3 \times 10^5$  per unit.

### Indications<sup>(6-11)</sup>

- To reduce the incidence of recurrent febrile non-hemolytic transfusion reactions (FNHTR). As much as 60% reduction in FNHTR incidence has been observed.
- To reduce HLA alloimmunization and HLA-mediated platelet refractoriness. A 50–80% lower incidence has been observed.
- To prevent transfusion transmission of intracellular pathogens such as cytomegalovirus (CMV) and Human T-Lymphotropic Virus, types I and II (HTLV- I/II). Reduction of viral load has been demonstrated for Epstein-Barr virus (EBV), without published clinical effectiveness data<sup>(12)</sup>.

### 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. The presence of residual donor leukocytes may result in microchimerism, which can lead to transfusion-associated graft-versus-host disease (TA-GVHD). For clinical situations with high risk for TA-GVHD, irradiation of cellular products is required<sup>(13)</sup>. (refer also to "Irradiated Components" section) or alternatively some pathogen reduced products may be approved for this purpose (see "Pathogen Reduction" section).

## 2. Cytomegalovirus (CMV) Reduced-Risk Components

### Description and Preparation of Components

CMV is an intracellular virus, transmissible by cellular blood components, that may have detrimental, potentially lethal, effects in immunocompromised patients. Of potential U.S. donors over age 17, 50–90% have been exposed to CMV<sup>(14)</sup>. Blood products that are considered to have reduced risk include the following: <sup>(15,16)</sup>

- CMV seronegative cellular blood components from individuals who test 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, donor antibody titers may decrease to undetectable levels, resulting in false-negative serostatus<sup>(17)</sup>.
- Leukoreduced cellular blood components. Residual risk may remain due to the presence of cell-free virus and/or residual infected WBCs in the product<sup>(15, 17, 18)</sup>.

### Additional Comments

- Frozen/deglycerolized RBCs that were collected and stored prior to the availability of modern leukoreduction filters may not be leukoreduced.
- Plasma products that have been frozen are not considered to represent a risk for CMV transmission.
- CMV reduced-risk components may not be 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 evaluated on a regular basis if the patient is seronegative pre-transfusion.
- Final determination of product choice may depend on product availability and patient need based on a risk/benefit analysis<sup>(19)</sup>.
- Pathogen inactivated blood products that reduce CMV are an alternative to CMV reduced risk components described above although side-by-side comparison studies are not available and are considered impractical<sup>(20)</sup>.

## 3. Irradiated Components

### Description and Preparation of Components

A severe and almost uniformly fatal consequence of transfused allogeneic leukocytes is transfusion-associated graft-versus-host disease (TA-GVHD), a reaction that occurs in a recipient incapable of mounting an immune response against foreign donor-derived white blood cells. Viable donor WBCs are capable of recognizing foreign (i.e., recipient) HLA antigens on tissues and organs and mounting a cellular immune response that damages recipient skin, liver, the gastrointestinal tract and other tissues<sup>(21)</sup>. Inactivation of donor lymphocytes by gamma- or X-irradiation can prevent the proliferation of transfused lymphocytes and the development of TA-GVHD. AABB-recommended irradiation exposure dosages consist of the following: Central portion of the container, to a minimum of Gy (2,500 cGy), with the remainder of the irradiation container receiving  $\geq 15$  Gy<sup>(2,3)</sup>.

If a patient requires irradiated products, all cellular products (e.g., RBCs, whole blood, apheresis granulocytes, whole blood-derived platelets, apheresis platelets, and liquid, i.e., never-frozen plasma) should be irradiated. Cellular products that may be a close HLA match (e.g. HLA-selected or crossmatched platelets, products from donors who are closely related) to the recipient should also be irradiated. TA-GVHD has not been reported in association with use of cryoprecipitate<sup>(22,23)</sup> or frozen plasma, thus irradiation of these components would not be required<sup>(24)</sup>.

The expiration date of irradiated RBCs is shortened to 28 days post-irradiation or the original expiration date, whichever occurs sooner. Irradiation has no known deleterious effect on platelets, and the expiration date remains unchanged<sup>(3)</sup>.

For patients who are sensitive to elevated extracellular levels of potassium that can accumulate during storage of irradiated RBC-containing units, removal of residual plasma by washing is recommended<sup>(25)</sup>.

## Indications<sup>(26,27)</sup>

- Intrauterine transfusion (IUT) 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), DiGeorge 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
- Allogeneic or autologous hematopoietic progenitor cell (HPC) transplant. HPC products MUST NOT be irradiated.
- Patient receiving T-cell suppression therapy including purine nucleoside analogs and antagonists (e.g., fludarabine, bendamustine, azathioprine, alemtuzumab, antithymocyte globulin)

## 4. Washed Cellular Components

### Description and Preparation of Components

Using an automated device, a cellular blood product (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<sup>(28)</sup>. Use of open systems, necessitates shortening the expiration to 24 hours for RBCs and four hours for platelets (whole blood-derived or apheresis). The overall product recovery yield, which is dependent on the type of automated blood cell processor and age of component, can result in an approximate cell loss of 20% for a RBC unit and 33% or more for platelet units<sup>(3,28)</sup>.

### Indications<sup>(24,29-31)</sup>

- Anaphylactic and recurrent significant allergic transfusion reactions that are 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 used less commonly due to logistical challenges of obtaining them in a timely manner.
- 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) which is severe congenital thrombocytopenia due to maternal anti-platelet antibody directed against a paternally derived fetal platelet antigen (e.g. HPA-1a). Maternal platelets from which antibody is removed by washing may be used, though logistical and medical problems collecting from the mother during the perinatal period often make this impractical. Frequently, platelets from recently tested platelet donors known to be HPA-1a negative or that can be crossmatched to maternal serum are used to manage NAIT.
- Recurrent febrile non-hemolytic transfusion reactions (FNHTRs) in patients unresponsive to leukocyte-reduced products and anti-pyretic pre-treatment.

### Additional Comments

- Bacterial contamination risk is introduced 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 of transfusion-associated graft-versus-host disease (TA-GVHD) is also unaffected by washing blood products.
- An alternative to washing RBC units when potassium is an issue is the use of fresher (e.g., <5-day-old) products.
- Because volume reduction may not adequately reduce the supernatant plasma proteins in platelet units, washing is preferred for the prevention of recurrent and/or severe allergic reactions and preparation of maternal units for patients with NAIT<sup>(30)</sup>.
- Intraoperative cell salvage devices can also be used to wash RBC units<sup>(31)</sup>.

## 5. Volume Reduction<sup>(1)</sup>

Volume reduction involves centrifugation of cellular products followed by aseptic removal of the supernatant which contains excess plasma and storage medium. In addition to decreasing volume, this process reduces the total amount of plasma proteins including antibodies. Some loss of platelet function through platelet activation may be anticipated but preservation of cellular functionality is maintained<sup>(27)</sup>. Maximum shelf-life is 24 hours at 1 to 6°C for RBCs or 4 hours at 20 to 24°C for platelets.

### Indications

Cellular components with reduced plasma volume may be used when the volume status of a patient is being aggressively managed, such as a fetus undergoing in-utero transfusion, infants with compromised cardiac function, or adults who may tolerate volume poorly. This approach may also be used to prevent or limit hemolysis when platelets with ABO-incompatible plasma are transfused. Volume reduction is not a substitute for washing or for dosing with small aliquots<sup>(1,2)</sup>.

## 6. Splitting<sup>(32)</sup>

If a sterile docking device or sterile entry into a single unit of thawed plasma and cryoprecipitate, RBCs or platelets is available, it may be possible to split units into aliquots, making it easier to provide smaller dosing. In addition, a single blood unit may be transfused over several days and therefore decrease donor exposure. Aliquots issued from the blood bank are to be subject to the same time limits as equivalent whole dose product. Blood providers may supply attached side bags to blood units which may facilitate this process<sup>(32)</sup>.

### Indications

- Patients who may benefit from smaller doses without increasing risk due to exposure to additional donors (e.g. neonatal/pediatric recipients).

### Additional Comments

- Adult patients receiving prophylactic platelets to prevent bleeding may potentially receive adequate doses from split products<sup>(33-35)</sup>.

## 7. Pathogen Inactivation/Reduction

Technology to inactivate pathogens is now available in the United States and is widely used in European countries. These methods prevent the replication and growth of a wide variety of viruses, bacteria and parasites by damaging genetic material (i.e., nucleic acids) or disrupting cellular membranes. When referring to the method to treat blood components for pathogens the term "Pathogen inactivation" is used. "Pathogen reduction" however is the intended effect of this modification to decrease the counts of microorganisms.<sup>(36)</sup> None of the current pathogen inactivation methods can completely eliminate all pathogens or assure sterility in a blood component, and all have an effect on component content.

### Pathogen-Inactivation Methods Approved in the United States

**Solvent-detergent (S/D) treatment (Octaplas, Pooled Plasma, Octapharma USA, Hoboken, NJ):** Each lot of Octaplas consists of pooling more than 600 individual plasma collected units, of a single ABO blood type. Using a non-ionic detergent [1% tri(n-butyl) phosphate (TNBP) and 1% octoxynol], the cellular lipid membranes of enveloped pathogens are disrupted in this inactivation process<sup>(39)</sup>. Because the treatment has no effect on non-enveloped viruses, the plasma pool is tested for Parvovirus B19 DNA and Hepatitis E Virus RNA, in addition to other applicable donor screening requirements and viral marker tests.

**Clinical Utility:** S/D Plasma is tested for coagulation factors II, V, VII, VIII, X, XI, Protein C, Protein S, alpha-2-plasmin inhibitor, fibrinogen and ADAMTS13. Protein S and alpha-2-plasmin inhibitor are sensitive to the S/D treatment, and the process is controlled to ensure that in the final product these factors are within the normal physiologic range. However, the product still contains a labeled warning for use with Protein S deficient patients, as historical experience with another S/D treated plasma product with lower levels of Protein S and alpha-2-plasmin inhibitor (<20%) identified thromboembolic complications<sup>(40)</sup>. S/D Plasma is approved for use in patients with acquired coagulation factor deficiencies (liver disease or liver transplant), cardiac

surgery, and thrombotic thrombocytopenic purpura. The product should be ABO compatible. Octaplas must be transfused within 24 hours if stored at 1-6°C or within 8 hours if stored at 20-25°C<sup>(41)</sup>.

- Amotosalen (synthetic psoralen compound, S-59) and photoactivation by UVA light (INTERCEPT Blood System for Platelets, Cerus Corporation BV, Amersfoort, Netherlands)

**Principle:** As of the writing of this chapter, INTERCEPT has been FDA approved for use with collected plasma and platelets. This pathogen inactivation system is a photochemical treatment process in which amotosalen (S-59, a psoralen derivative), a chemical capable of covalent binding to nucleic acids, is added to plasma or platelets<sup>(42,43)</sup>. Upon exposure to UVA illumination, the amotosalen induces covalent crosslinking of bound nucleic acids, thereby blocking further cellular replication.

**Clinical Utility of Plasma:** All coagulation factors, including Protein S and alpha-2-plasmin inhibitor, are present in the treated plasma with only minor differences (~15%) in levels compared to conventional components. INTERCEPT plasma has provided comparable hemostatic support to patients with acquired coagulation factor deficiencies (liver disease or liver transplant) and in treating patients with thrombotic thrombocytopenic purpura.

**Clinical Utility of Platelets:** Platelet collections treated with the INTERCEPT Blood System for Platelets and stored for five days retained mean platelet doses that are predicted to be therapeutically effective. 43

## Indications

See individual blood component indications in the respective chapters of this text.

## Contraindications

INTERCEPT plasma and platelets: patients with a history of hypersensitivity reaction to amotosalen or other psoralens and neonatal patients treated with selected phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth < 375 nm (Intercept USA Package Insert). A precaution on the label warns that INTERCEPT plasma may cause cardiac events ranging from rate or rhythm disturbances<sup>(44)</sup> to angina pectoris<sup>(40)</sup> or cardiac arrest<sup>(45,46)</sup>. In addition, a randomized trial for recipients of INTERCEPT platelets observed an increased incidence of Acute Respiratory Distress Syndrome (ARDS)<sup>(41)</sup>.

## Additional Comments

- Several pathogen inactivation systems are not approved by FDA for use in the United States but have met regulatory requirements in the European Union. In addition, pathogen inactivation methods for red cells and whole blood are actively under investigation in clinical research studies.
- Pathogen reduction by the INTERCEPT Blood System for Platelets is also accepted by the FDA as an alternative for irradiation.

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# The Hospital Transfusion Committee



## Overview

Patient Blood Management's aim is to develop indicators for blood usage to optimize the patient's blood counts while reducing risks from inappropriate product transfusion and medical error. This is enforced through an evidence-based and multi-disciplinary approach that is led by an established overarching body referred to as an institutional transfusion, blood utilization or hospital transfusion committee.

To ensure the safety and efficacy of transfusion, accrediting agencies including AABB and the College of American Pathologists (CAP) require hospitals to monitor blood transfusion practices and adverse events. The Joint Commission (TJC) and the Code of Federal Regulations (CFR) mandate that hospitals develop, implement, and maintain an effective, data-driven quality assessment and performance improvement program. If Medicare reimbursement is sought, it is understood that hospitals are obliged to have such programs in place.

The hospital Transfusion Committee exists to ensure compliance with regulatory and accreditation requirements, optimize transfusion practices to local clinical activities, reduce adverse events, all the while doing so in a cost-effective manner. The committee collaborates with medical leadership to establish evidence-based transfusion guidelines, support a quality infrastructure to monitor transfusion practices, and support the Patient Blood Management (PBM) program. The committee works with medical leadership to address physician non-conformance with hospital transfusion guidelines<sup>(2,4-6)</sup>.

Large healthcare institutions may have resources to support a free-standing Transfusion Committee; however, it is not unusual in smaller institutions to utilize alternate subcommittees such as those for Pharmacy or Quality to function in lieu of a Transfusion Committee. Regardless, the roles and responsibility for transfusion practice and oversight described in this chapter apply.

## Membership

In order to understand the blood-ordering practices, to maximize visibility and influence, the committee must be multidisciplinary and have representation not just from the transfusion service but also from departments that routinely order blood, such as anesthesiology, emergency medicine, and hematology<sup>(10,11)</sup>.

The Transfusion Committee should meet regularly (e.g., quarterly basis) to ensure timely response to identified topics. Member attendance or their assigned delegate(s) is required.

At a minimum, the Transfusion Committee should include the following identified roles<sup>(13)</sup>:

- Chairperson. A physician knowledgeable on contemporary transfusion practices. An individual who has the authority and influence to make effective change within the organization's medical community
- Transfusion Service representation such as the Clinical Laboratory Medical Director, Laboratory Director, or Laboratory Manager
  - Serve as the primary liaisons between the transfusion and clinical care services
  - Report on adverse events
  - Report on transfusion errors and near misses such as improperly labeled samples
  - Report on issues that may have an impact on blood bank inventory or services (e.g., blood shortages, reagent shortages or software upgrades)
  - Report on metrics such as blood utilization, product outdates and wastage
  - Provide updates on technology (e.g., pathogen reduction or coagulation point-of-care testing instruments), products, and practices for improving transfusion safety

- Departmental representatives that order and/or transfuse blood products: physicians, perfusionists, nurses, and other health care professionals such as physician assistants or nurse practitioners
- Ancillary services such as pharmacy, risk management
- Quality assurance
  - Perform period internal audits with electronic or manual record review as well as related time observation of transfusion processes
  - Monitor for trends or ordering patterns and compliance with transfusion guidelines
- Local blood provider can serve in a consulting capacity
- Secretary to record and distribute meeting minutes, track member-assigned project deadlines, and coordinate meeting schedules
- Transfusion Safety Officer/Coordinator
  - Reports data pertaining to current transfusion practices, including feedback on activities related to compliance with transfusion guidelines, and hemovigilance
  - Identify educational opportunities defined by non-conformance events
  - Identify barriers to implementing recommendations

Provide feedback on the implementation of Transfusion Committee standards: this may be performed through review of electronic medical records for automated identified alerts associated with transfusion practices through the CPOE (computerized physician ordering entry)] as well as monitoring patient outcomes<sup>(1,3, 12, 13).</sup>

## Functions

The Transfusion Committee's scope of responsibility extends well beyond reviewing and responding to blood utilization trends. It also advocates a culture to promote proper blood utilization and reduce errors and near-misses.

The key function of the Transfusion Committee is to promote best practices in transfusion. This is accomplished by establishing institutional guidelines and policies, facilitating educational opportunities for ordering and transfusing staff, and overseeing blood utilization through internal assessments and quality audits.

### **The following is a list of Transfusion Committee responsibilities<sup>(2,4,8,9,14)</sup>:**

- Blood administration policy and procedure development
  - Institutional guidelines should be periodically reviewed and updated to the most current evidence derived from randomized controlled trials and/or professional society.
  - Criteria selected should appropriately meet the facility's patient demographics.
- Patient blood management
  - Appropriateness of blood product utilization
  - Turnaround times for emergency requests
  - Massive transfusion protocols: frequency of implementation, ratio of issued products
  - Type O and/or RhD negative red blood cells usage
  - Autologous blood product usage
  - Blood utilization trend analysis for cross-match:transfusion ratio, usage and discard rates
  - Patient outcome analysis
  - Identification and implementation of clinical alternatives to blood transfusion (e.g., erythropoietin, perioperative blood recovery)
  - Promotion of new services and blood products (e.g., platelet additive solution (PAS) platelets)
  - Promotion of technologies such as clinical decision support services (CDSS) and computerized online entry (CPOE) to influence ordering practices in real time
  - Promotion of software or web-based technologies to monitor and benchmark transfusion practices of individual physicians and specialty groups

- Compliance and regulatory oversight
  - Evaluate policies
  - Define internal audit metrics
  - Report external and internal audit survey results
  - Report infectious and non-infectious adverse events
  - Track medical errors, near-misses and sentinel events.
  - Participate in follow up actions on transfusion-associated fatalities and biological product deviations reported to the FDA and other governing and accrediting agencies
  - Monitor corrective actions for non-compliant activities
  - Staff training and education
  - Promote Transfusion Committee standards of practice, regulations, and/or accrediting organizations
  - Develop communication processes to provide updates on transfusion related information
  - Oversee development and implementation of training modules or alternative education venues such as staff meetings, grand rounds, interactive laboratory and transfusion practice sessions
  - Provide resources for continuing education to be incorporated into the institution's Continuing Medical Education (CME) and Continuing Education (CE) curricula
  - Serve as department liaison to share relevant Transfusion Committee information

## Reports

Information presented to the Transfusion Committee should be consolidated into a standard reporting format. This would include review of those activities mentioned in the previously mentioned 'Process' section, for example, transfusion service data, transfusion practice audits, and project updates. This facilitates on-going assessment of blood administration practices. Trends in blood utilization, inventory management, and cost can be identified and analyzed on a regular basis.

Minutes and reports should be submitted by the secretary to other committees such as Medical Executive or Credentialing committees. This is to provide other peer-review committees with a record of actions to ensure appropriate transfusion-related patient care. Minutes may be protected from inappropriate legal discovery as a critical component of the institution's quality monitoring program.

Situations in which blood administration deviates from the institution's policies and procedures should be investigated by the committee in collaboration with the leadership of the involved department and quality assurance<sup>(11,15)</sup>.

## The Transfusion Committee and Patient Blood Management

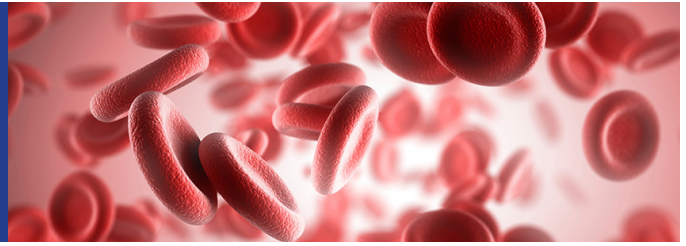
The adoption of Patient Blood Management by many hospitals strengthens the role of the Transfusion Committee in promoting safer transfusion.

*Please refer to the Patient Blood Management chapter.*

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# Patient Blood Management



## Introduction

Transfusion of the appropriate blood component in the appropriate setting can be a life-saving medical intervention, but because of inherent risks should be administered only when clinically necessary and ideally, evidence-based. Blood is a vital but limited resource. Good stewardship is therefore essential to ensure blood availability when transfusion is truly indicated. Patient Blood Management (PBM) is a multifaceted discipline that encompasses this concept. This chapter:

- Defines PBM
- Discusses the essential elements of a successful program
- Presents approaches to perioperative blood management

*Specific blood components are discussed in other chapters.*

## Rationale for Patient Blood Management

Blood transfusion is the most commonly performed medical procedure, occurring with 11 percent of patients<sup>(1)</sup>. In 2013, the American Hospital Association identified blood utilization in inpatient services as one of five areas for hospitals to focus on to reduce non-beneficial care<sup>(2)</sup>. Per capita transfusions in the US are higher than in other Western countries, and practices vary widely<sup>(3)</sup>. In one report, RBC transfusion rates in similar patient populations ranged from 9 to 92% in orthopedic surgery, 17% to 82% in colorectal surgery, 20% to 53% in critical care and up to 28% in acute coronary syndrome<sup>(4)</sup>. Patient outcomes were not significantly different, suggesting that some transfusions may have been avoidable and possibly offered no clinical benefit, yet may have exposed the patient to risk. Evidence of hospital-specific variability in transfusion rates for adult patients undergoing coronary artery bypass graft (CABG) surgery was described in the Journal of the American Medical Association (JAMA) and showed that RBC transfusion rates varied from 7.8% to 92.8%, platelet transfusion from 0.4% to 90.4%, and plasma use was as high as 97.5%<sup>(5)</sup>.

The risks of allogeneic transfusion are well established and include but are not limited to transmission of infectious diseases and the occurrence of non-infectious complications such as alloimmunization, hemolysis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and anaphylactic reactions. A growing body of evidence suggests that RBC transfusions may be associated with unfavorable outcomes such as increased risk of patient morbidity and mortality<sup>(6)</sup>. Glance et al. performed a retrospective analysis of the association between intraoperative blood transfusion and 30-day morbidity and mortality in patients undergoing general, vascular, or orthopedic surgery. Patients receiving an intraoperative transfusion of one or more units of red blood cells had a higher risk of mortality and were more likely to have pulmonary, septic, thromboembolic, and wound complications<sup>(7)</sup>.

*For side effects and hazards, please see the Appendices.*

The possibility that patients are unnecessarily exposed to transfusion risks is reinforced by reports from the American Medical Association and The Joint Commission (TJC) with the Centers for Medicare and Medicaid Services that identified RBC transfusions as one of the top five overused procedures in medicine<sup>(8)</sup>. Supplemental findings from the National Blood Collection and Utilization Surveys (NBCUS) found that 92.7% of respondents reported having transfusion guidelines<sup>(9)</sup>, but at least one audit of transfusion practices performed in 2011 indicated that 40%-60% of transfusions were inappropriate and given outside of guidelines<sup>(10)</sup>.

The above discussion demonstrates the need for a formal process to guide transfusion decisions and, ultimately, improve patient care. PBM is defined by the AABB as “an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion<sup>(9,11)</sup>” It is wide-ranging and includes transfusion therapy based on robust evidence to maximize a patient’s oxygen-carrying capacity, minimize blood loss in surgical and trauma settings, and integrate alternative therapies, when available, into PBM practices<sup>(12)</sup>. Benefits of PBM include fewer transfusions, the avoidance of potential complications<sup>(13)</sup>, decreased length of hospitalization, fewer readmissions and a subsequent reduction in the many associated costs<sup>(14)</sup>.



AABB has provided an important framework for PBM that is supported by its PBM Standards and PBM Accreditation Program<sup>(15)</sup>, yet the supplemental findings from the NBCUS, 2013, 2015 and 2017 reported that only 50.3 % of responding hospitals had a PBM program<sup>(9)</sup>. The 2017 NBCUS noted an ongoing but slowing decline in both blood collection and blood utilization in the United States<sup>(76)</sup>. The decline in number of transfusion was significant with RBC, PLT and plasma transfusions decreasing 13.9 %, 13.1%, 24.8% respectively. (A) It is important to note that TJC has leveraged its authority as a hospital accreditation organization to influence transfusion oversight and practices, and is expanding beyond previously established Performance Measures to collaborate with AABB in offering PBM certification

Elements of an effective and successful PBM program are<sup>(15, 16)</sup>:

- Commitment
- Leadership
- Program oversight
- Transfusion practice guidelines
- Integration of information technology Non-compliance with transfusion guidelines

## **Commitment**

Commitment of an organization to developing and implementing a PBM program is essential and maximizes the potential for success. Without it, efforts to improve transfusion practices and safely minimize transfusion may not realize their full potential, or even flounder. The provision of financial resources for information technology, infrastructure, staffing, education, consistent messaging, and continuing focus on patient safety all characterize commitment.

## **Leadership**

High-level medical, nursing, and executive leaders who will advocate for evidence-based changes in practice and financial resources should serve on a PBM steering or program development committee. Other stakeholders would include medical and surgical departments that routinely order and transfuse blood, the hospital transfusion committee, transfusion and laboratory medicine, pharmacy, quality assurance, and risk management. If the institution has a Transfusion Safety Officer, that individual should participate as well.

*Please refer to the Hospital Transfusion Committee chapter*

## **Program Oversight**

The organization should create a transfusion oversight entity to establish, monitor, promote and enforce PBM activities through audits, periodic updating of transfusion guidelines, advocacy of educational initiatives, communication with clinical and nursing staff, and continuous review and process improvement. This requirement may be met by a transfusion or stand-alone PBM committee or other committee charged with comprehensive PBM responsibilities. Optimally this multidisciplinary group should include representatives from departments that participate in the steering committee.

## **Transfusion practice guidelines**

The organization should develop or update institutional transfusion guidelines that are based on credible evidence, current peer-reviewed literature, and/or guidelines published by professional societies. Many of these resources are provided in specific blood component sections of this Compendium and will not be covered in depth here.

## **Role of information technology in PBM**

Information technology is increasingly recognized as an essential PBM tool that provides evidence-based transfusion recommendations in real time and enables extraction of benchmarking data for individual physicians and service lines<sup>(16)</sup>. Utilization audits can be facilitated by software designed for generating orders. Computerized physician order entry (CPOE) and clinical decision support systems (CDSS) represent established and effective IT approaches for monitoring transfusion practices<sup>(17)</sup>.

Rana et al. first described the use of CPOE with CDSS for red cell transfusions in critically ill adults. The CPOE configuration prompted ordering physician to select an indication for red cell transfusion when the pre-transfusion hemoglobin was greater than 7 g/dL in adult intensive care patients. The study showed that in the initial three months after implementation of CPOE

with CDSS, a decrease in RBC transfusions of approximately 15 % and a decrease in transfusion-related complications were observed<sup>(18)</sup>. Lin et al. described the results of a hospital-wide CPOE system that was configured to prompt the ordering physician to select from a list of appropriate transfusion indications when ordering platelets<sup>(19)</sup>.

PBM-based blood order sets can be integrated into the hospital's ordering system and evidence-based transfusion guidelines and alerts hardwired into the CPOE system. Data collection and monitoring can be facilitated. In addition, CPOE provides automated, real-time clinical practice guidance when the physician is interfacing with the system to order blood<sup>(20)</sup>.

CPOE alerts are effective in reducing orders that may not meet guidelines. Rothschild et al. evaluated ordering practices prior to and post implementation of a CPOE-based CDSS. Their CPOE system had an "adaptive alert" capability that enabled the CPOE system to interact with the laboratory information system. Laboratory parameters were queried and transfusion recommendations were provided based on clinical information and laboratory test results. Results showed a decrease in inappropriate orders<sup>(21)</sup>.

Baer et al. described the implementation of an electronic transfusion ordering and monitoring system with guidelines for the neonatal intensive care unit (NICU). This resulted in an increase in compliance from 68% to 90%<sup>(22)</sup>. Yerrabothala et al. described the utilization of CPOE with a CDSS system to support the establishment of evidence-based restrictive transfusion guidelines for RBC transfusion. The study had an approved transfusion trigger of 7 g/dL with additional indications for special populations, such as actively bleeding patients or patients with a history of acute myocardial infarction. The study showed a statistically significant decrease in the pre-transfusion hemoglobin and in RBC transfusions per 1000 patient days<sup>(23)</sup>.

Other features that influence the effectiveness of CPOE with CDSS include user involvement in the development phase, the capability to provide alternate recommendations at point-of-order, and integration with the medical record or order entry system<sup>(24)</sup>.

## Addressing outliers

Accredited hospitals are required by AABB, CAP, and TJC, and possibly other oversight organizations, to perform blood utilization review. Despite findings from randomized controlled trials and updated transfusion recommendations based on peer-reviewed published data, clinician knowledge gaps remain. Continuing education of physicians about evidence-based transfusion guidelines may modify transfusion practices. Strategies for continuing education could include transfusion medicine participation in clinical rounds, audits with specific feedback, and one-on-one discussions with the department chair/designee or the Transfusion Safety Officer, continuing medical education (CME), and electronic or hard-copy dissemination of hospital transfusion guidelines<sup>(25)</sup>.

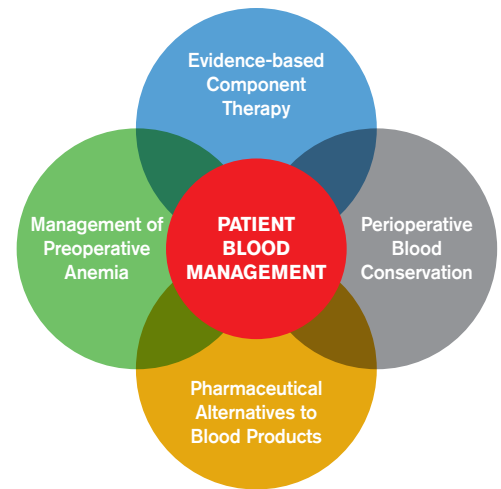
Retrospective monitoring of transfusion practices using hard-copy medical records is still in use, and results are presumably reported to an institutional oversight committee for evaluation and follow-up actions. Limitations of this approach include the potential for statistically unsubstantiated selection of documents for review, untimely feedback to physicians, inconsistent review processes, occasional inaccurate identification of physicians who actually ordered the blood, and the inability to prevent unnecessary transfusion<sup>(26)</sup>. If audits can be performed within days of transfusion and are combined with strategies such as education, it may be feasible to decrease utilization<sup>(27)</sup>. Sarode et al. used a combination of institution-wide education and prospective review to achieve significant cost savings by decreasing inappropriate RBC and platelet utilization by 60% and 25% respectively<sup>(28)</sup>. Toy found that one-on-one meetings with physicians, scheduled teaching conferences, prospective audits of ordered transfusions, in addition to daily clinical rounds, were useful<sup>(29)</sup>.

While such approaches may potentially impact clinician behavior, they are labor intensive and impractical for some hospitals. Further, real time interventions in ordering may cause a delay in issuing blood products. Meaningful effective change requires continuous monitoring and the collection of ordering and transfusion practice data<sup>(30)</sup>. Physicians and physician groups who routinely order outside of established hospital guidelines can be made aware of this through data sharing and comparison of their practices with physicians of the same specialty. Subsequent interventions to address outlier ordering behavior include peer interaction or targeted education or feedback from medical committees and department chairs.

## PBM in the Perioperative Setting

According to the 2013 AABB Blood Collection, Utilization and Patient Blood Management Report, approximately 21% of RBC units and 18% of platelet units were transfused in surgical settings<sup>(9)</sup>.

As an inherently invasive process, surgery presents special challenges with respect to potential bleeding and blood loss. Achieving the PBM goals of reducing or eliminating transfusion requires approaches that are unique to this setting and includes identification and management of preoperative anemia and reduction of perioperative blood loss. For a comprehensive perioperative PBM framework, the reader is referred to guidelines from the American Society of Anesthesiologists and the Network for Advancement of Transfusion Alternatives, and others<sup>(31-33)</sup>.



### Identification and management of preoperative anemia

Anemia is defined by the World Health Organization (WHO) as a hemoglobin level less than 12 g/dL for adult females and less than 13 g/dL for adult males.

Undiagnosed anemia is common and can be a major predictor of perioperative transfusion, depending on the type and complexity of the surgical procedure. Preoperative anemia and perioperative transfusion are both independently associated with increased postoperative morbidity and mortality and length of hospitalization. One US audit of patients undergoing elective orthopedic surgery found that 35% were anemic on preadmission evaluation.<sup>(34)</sup>

The causes of preoperative anemia are varied and include older age, co-morbid conditions (cardiac and pulmonary disease), anemia of chronic disease, nutritional deficiencies, and blood loss. The most common cause of preoperative anemia is functional iron deficiency for which intravenous iron supplementation is the recommended therapy.<sup>(35)</sup>

Screening of patients for preoperative anemia should be routinely performed and would include a CBC with reticulocyte count, assessment of iron status (serum iron ferritin, transferrin saturation), vitamin B12 and folic acid levels, with additional testing and evaluation as indicated. Specific treatment would be targeted to address the cause, and as indicated, could include iron administration, erythropoietin-stimulating agents (ESAs), vitamin B12 and folic acid administration, for example. Specific comment is provided below on the use of iron and ESAs.

### Iron therapy for iron-deficiency anemia

Oral iron has been a long-prescribed, low cost treatment, but low bioavailability and poor intestinal absorption are problematic. Because it may be associated with gastrointestinal side effects and thus poorly tolerated, patient compliance may be suboptimal. Intravenous iron has been shown to be effective in correcting anemia and causes fewer gastrointestinal side effects. Studies show good evidence of safety and efficacy in the perioperative setting. Iron sucrose and iron gluconate are examples of current formulations that are deemed safer, with fewer concerns about the potential for anaphylaxis<sup>(36)</sup>.

### Erythropoietin-stimulating agents (ESAs)

Erythropoietin-stimulating agents (ESAs) are highly effective in increasing hemoglobin levels<sup>(37)</sup>. A systematic review of randomized trials evaluating preoperative erythropoietin efficacy in patients undergoing orthopedic and cardiac surgery showed a reduction in the number of patients receiving allogeneic transfusions<sup>(38)</sup>. A meta-analysis evaluating patients undergoing cardiac surgery showed that patients receiving preoperative erythropoietin had a significant reduction in the need for transfusion<sup>(39)</sup>. A combined regimen of erythropoietin and intravenous iron has been shown to enhance the response to erythropoietin<sup>(40)</sup>.

It is important to note that ESAs are linked to increased mortality and thromboembolic risk. Consideration of their use should be based on an appropriate risk-benefit analysis. It is recommended that ESAs be used conservatively, with close monitoring<sup>(36, 41-43)</sup>.

### Patient Blood Management Evidence-Based Recommendations

An International Consensus Conference on Patient Blood Management was convened in Frankfurt, Germany in April 2018. The objective of the meeting was to develop a set of evidence-based recommendations for patient blood management (PBM) and for research. The scientific committee developed 17 Population/Intervention/Comparison/Outcome (PICO) questions for red blood cell (RBC) transfusion in adult patients in 3 key areas:

1. Preoperative anemia
2. RBC transfusion thresholds
3. Implementation of PBM programs

The PICO questions guided the literature search in 4 biomedical databases (MEDLINE, EMBASE, Cochrane Library, Transfusion Evidence Library) which searched from inception to January 2018.

Data from 145 studies, including 63 randomized clinical trials and 82 observational studies were evaluated. The conference developed the following recommendations:

### **1. Preoperative anemia:**

- Strong recommendation to detect and manage anemia sufficiently early before major elective surgery.
- Conditional clinical recommendations: Preoperative anemia
  - Use of iron supplementation to reduce red cell transfusion rate in adult pre-operative patients with iron-deficient anemia undergoing elective surgery.
  - Do not use erythropoiesis-stimulating agents routinely in general for adult preoperative patients with anemia undergoing surgery.
  - Consider short-acting erythropoietins in addition to iron-supplementation to reduce transfusion rates in adult preoperative patients with hemoglobin concentrations < 13 g/dL undergoing elective major surgery.

### **2. RBC transfusion thresholds**

- Strong clinical recommendation 1- For critically ill but clinically stable intensive care patients with or without septic shock (recommended threshold for RBC transfusion, hemoglobin concentration < 7 g/dL).
- Strong clinical recommendation 2- For patients undergoing cardiac surgery (recommended threshold for RBC transfusion, hemoglobin concentration < 7.5 g/dL).
- Conditional clinical recommendations: Red Blood Cell Transfusion Thresholds
  - Restrictive transfusion threshold (hemoglobin concentration < 8 g/dL) in patients with hip fracture and cardiovascular disease or other risk factors.
  - Restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding.

### **3. Implementation of PBM programs**

- Conditional recommendations to improve appropriate RBC utilization
  - Implement comprehensive PBM programs
  - Use electronic decision support systems

Overall, 10 clinical and 12 research recommendations for preoperative anemia, RBC transfusion thresholds for adults and implementation of PBM programs were established. The conference noted the relative paucity of strong evidence to answer many of the PICO questions. Further, they supported the need for additional research and an international consensus for accepted definitions and hemoglobin thresholds as well as clinically meaningful end points for multicenter trials <sup>(77)</sup>.

Among the challenges outlined in the Frankfurt consensus was the lack of data to guide clinical practice for patients with hematologic and oncologic conditions as well outcome data for older patients regarding quality-of-life or rehabilitation potential in regard to hemoglobin levels postoperatively or post discharge from the hospital.

A recent prospective, observational study, the Red Cells in Outpatients Transfusion Outcomes study (RETRO) assessed the effects of RBC transfusion on the functional status and quality of life in 221 older adult hematology/oncology patients in the outpatient setting. Patients whose hemoglobin levels were maintained at 8 g/dL or greater at 1-week posttransfusion and who had neither received recent cancer treatment nor required hospitalization demonstrated clinical improvement in two functional status measures the 6-minute walk test and fatigue score<sup>(78)</sup>.

A retrospective chart review by Gehrie et al assessed platelet dosing in 602 adult oncology outpatients. Transfusion indices after 1 unit and 2 units of apheresis platelets were evaluated to determine whether there was a benefit to transfusion of 2-units. The results of the study demonstrated that the transfusion of 2 units of platelets to adult oncology outpatients had no durable improvement in either platelet count or impact the subsequent transfusion schedule<sup>(79)</sup>.

### **Preoperative autologous donation**

Preoperative autologous donation (PAD) may be considered for planned elective surgical procedures associated with an anticipated risk of significant blood loss and for patients for whom it may be difficult to expeditiously provide compatible blood. Such patients would include those with antibodies to high frequency antigens and those with multiple alloantibodies. However, PAD is not recommended for surgical patients in other categories<sup>(44, 45)</sup>.

Although PAD has a role, albeit a limited one, for minimizing exposure to allogeneic blood, associated risks must be considered. A 2001 Cochrane review of 14 randomized controlled trials (RCTs) showed a mean decrement in the preoperative hemoglobin of approximately 1.1 g/dL in the PAD group compared to the non-PAD group, with an associated 24% increased risk of transfusion among patients in the PAD arm<sup>(46)</sup>. If PAD is ordered, prescription of iron supplements should be considered to enhance erythropoiesis in the perioperative and postoperative periods. Although AABB Standards permit PAD in patients with a hemoglobin as low as 11.5g/dL, it should be noted that each donation may either cause preoperative anemia or worsen pre-existing anemia. In addition, although perceived as being a safer alternative to allogeneic RBCs, units may be lost due to collection or processing problems, and complications such as TACO can occur. Further, the frequency of outdating for PAD units approached 45% in one publication<sup>(47)</sup>.

### **Anticoagulant and anti-platelet therapy**

The perioperative management of patients who are receiving antithrombotic anticoagulant and/or anti-platelet therapy is a frequent and often challenging situation for clinicians. New oral anticoagulants (NOACs) such as dabigatran, a direct thrombin inhibitor, and rivaroxaban, a direct factor Xa inhibitor, introduce additional complexity to perioperative blood management. (In October 2015, the U.S. Food and Drug Administration (FDA) approved idarucizumab, a monoclonal antibody fragment that directly binds dabigatran for the urgent reversal of the anticoagulant effects of dabigatran in emergency situations)<sup>(48)</sup>. Currently, there are few clinical trials that provide definitive guidance regarding best practices. The experience of Sarode may provide assistance in some circumstances<sup>(49)</sup>.

Decisions regarding perioperative management of patients receiving antithrombotic therapy can be guided by an assessment of thromboembolic risk versus risk of perioperative bleeding<sup>(50)</sup>. Guidelines from the American College of Chest Physicians stratify patients into the following thromboembolic risk categories:

- High risk (>10% annual risk for thromboembolism).
- Moderate risk (5-10% annual risk for thromboembolism).
- Low risk (<5% annual risk for thromboembolism).

Consideration regarding use of bridging therapy is often required for patients at greater risk for thromboembolism. Bridging therapy is commonly defined as the use of a short acting anticoagulant such as unfractionated heparin or low molecular weight heparin (LMWH) during the period of time that warfarin is being withheld. Observational studies with a systematic approach to perioperative anticoagulant management showed lower rates of thromboembolic and bleeding episodes<sup>(51)</sup>.

The American College of Chest Physicians recommends the following processes for inclusion into a standardized perioperative management protocol:

- Assessing patients at least 7 days preoperatively to plan perioperative anticoagulant management.
- Developing a schedule with the timing of warfarin and anti-platelet drug discontinuation and resumption, dose and timing of LMWH bridging, and the INR measurement schedule.
- Ensuring that the perioperative management strategy for vitamin K antagonists and anti-platelet drug interruption and initiation of LMWH bridging accounts for pharmacokinetics and thromboembolic and bleeding risks.
- Training of the patient or caregiver to administer LMWH.
- When indicated and feasible, performing INR testing on the day before surgery to identify patients with INRs that are elevated enough to presumably allow timely administration of vitamin K--Assessing hemostasis, preferably on the day of surgery and on the first postoperative day, to facilitate safe resumption of anticoagulant drugs<sup>(50)</sup>.



## Intraoperative blood management

Intraoperative blood management strategies generally focus on minimizing blood loss, collecting and reinfusing blood from the operative field, and improving tolerance of anemia. These approaches are generally considered standard practice.

### Acute normovolemic hemodilution (ANH)

ANH is a blood conservation technique that may be considered when significant blood loss is anticipated during the surgical procedure. The procedure is performed in the operating room immediately prior to surgery and involves the simultaneous removal of a specific volume of whole blood and replacement with crystalloid or colloid solution to maintain adequate volume. A dilutional anemia is created, reducing surgical blood loss. Blood collected by ANH is stored at room temperature and returned to the patient within 8 hours, possibly preserving the function of platelets and coagulation factors. The benefits of ANH have not been firmly established and disparate results have been reported<sup>(52,53)</sup>.

### Autologous red blood cell recovery

Autologous blood recovery (previously referred to as “salvage”) is another blood conservation technique that may be considered for surgical procedures in which substantial blood loss (greater than 1000 mL) is expected<sup>(75)</sup>. The procedure involves the collection of red blood cells from the surgical field. In intraoperative salvage, blood that is collected from the surgical field is centrifuged, washed, filtered and suspended in normal saline for reinfusion. The hematocrit is 45% to 55%. The minimum volume for reinfusion is 200 mL which is roughly equivalent to one RBC unit. This technique is often used in vascular, cardiothoracic, orthopedic, gynecologic and urologic surgery. Cell recovery has been shown to decrease the need for allogeneic transfusion<sup>(54)</sup>.

## Pharmacologic Agents

### Antifibrinolytic drugs

Antifibrinolytic drugs may be useful for reducing perioperative blood loss. Antifibrinolytic drugs act by inhibiting the fibrinolytic system which has a major role in controlling clot formation and dissolution. Tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) are lysine analogues that reversibly inhibit fibrinolysis by interfering with plasminogen activation. A Cochrane review determined that antifibrinolytics provided significant reduction in perioperative blood loss and the need for allogeneic transfusions without serious adverse effects<sup>(55)</sup>. The results of a literature review by Ortmann et al. showed that the use of TXA prophylactically reduced perioperative blood loss in cardiac and non-cardiac major surgery<sup>(56)</sup>. In the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial, 20,000 trauma patients were randomized to receive either TXA or placebo. Results of the trial showed that early administration of TXA (within 3 hours) was associated with reduced mortality<sup>(57)</sup>.

Aprotinin is a serine protease inhibitor that inhibits fibrinolysis by directly inhibiting plasmin. A multicenter trial showed an increase in mortality with its use, and it was withdrawn from the market. However, subsequent reevaluation of data from the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study and other data resulted in its reintroduction and use for cardiac surgery in Canada and Europe<sup>(58)</sup>.

### Topical Hemostatic Agents

Several commercially available, virally inactivated, allogeneic sealants and autologous fibrin sealant systems are FDA-approved and are preferable to cryoprecipitate with respect to safety and efficacy for topical use<sup>(59-61)</sup>. A Cochrane review showed a 37% reduction in allogeneic RBC transfusion and reduced blood loss when fibrin sealant was used<sup>(62)</sup>. Evaluation of 124 patients undergoing total knee arthroplasty in a randomized trial showed that topical application of TXA resulted in a 20%-25% reduction in postoperative blood loss without report of adverse effects<sup>(63)</sup>.

### Point of Care Testing

Steurer and Ganter describe three primary testing methods for point of care assessment of coagulation:

- Simple anticoagulation monitoring devices for activated clotting time (ACT), whole blood PT/INR and whole blood aPTT.
- Point of care coagulation tests to assess primary hemostasis and platelet function, for example, PFA-100/200 and modified platelet aggregometry.

- Viscoelastic coagulation monitoring devices that assess global clotting processes from initial thrombin generation to maximum clot formation and ultimately clot lysis. Thromboelastography (TEG; Haemonetics Corp., Braintree, MA) and rotational thromboelastometry (ROTEM, International GmbH, Munich, Germany) are commonly used platforms<sup>(64)</sup>.

## Viscoelastic Coagulation Technology

According to the 2013 AABB survey on blood utilization, RBC transfusion in cardiac surgery patients accounted for 7% of all RBC transfusions<sup>(9)</sup>. The hemostatic management of patients undergoing cardiovascular surgery may be challenging, and requires balancing anticoagulation during cardiopulmonary bypass with management of hemostatic function after the procedure has been completed. Conventionally, transfusion algorithms use standard coagulation tests such as platelet count, PT, aPTT and the Clauss fibrinogen assay to screen for coagulation abnormalities and guide treatment.<sup>(65)</sup> Turnaround times may not be optimal, and poor predictive value for bleeding limits their clinical utility, leading clinicians to make empirical decisions<sup>(66-68)</sup>. Increased interest in the use of viscoelastic point of care testing (POCT) has been driven in part by the limitations of conventional assays for hemostasis. Thromboelastography differs from conventional coagulation tests in that it uses whole blood to produce a two dimensional, computer-generated tracing in real time that provides information about the development, stabilization and dissolution of clots<sup>(69)</sup>. This tracing also provides a comprehensive composite view of the interaction of coagulation factors, platelets, fibrinogen, and rapid assessment of thrombosis and fibrinolysis<sup>(70)</sup>. TEG measurement of clot strength is important in determining whether intraoperative bleeding is due to coagulopathy or other causes and, as such, has a major role in TEG-based transfusion algorithms<sup>(71)</sup>. Randomized clinical trials indicate that use of TEG-based decision algorithms during cardiac surgery resulted in fewer transfusions<sup>(72)</sup>.

Viscoelastic coagulation monitoring instruments have become important tools in the POCT hemostatic assessment of patients, and have been implemented in many institutions<sup>(65)</sup>. TEG based transfusion algorithms have also been shown to improve blood utilization in liver transplant patients<sup>(73)</sup>, cardiac patients<sup>(74)</sup> and in major trauma patients in conjunction with massive transfusion protocols<sup>(75)</sup>.

When considering implementation of POCT, operational and quality considerations should include the logistical challenges associated with the need for rapid assay initiation, the need for daily calibration, and delineation of roles in interpreting results.

## Summary

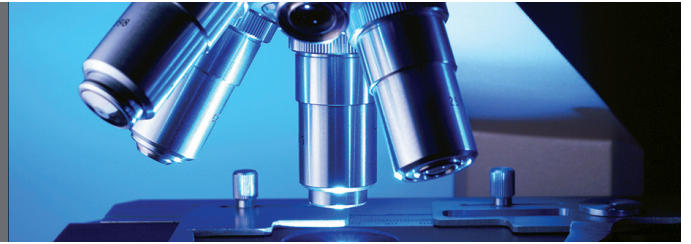
Patient blood management is a patient-centered, evidence-based approach to transfusion practice, with the overall goal of improving patient outcomes. It is now the standard of practice and care. Successful implementation of an effective patient blood management program has been shown to improve outcomes, reduce transfusion rates, and decrease associated costs.

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## Appendices



### Appendix I: Side Effects and Hazards for Whole Blood and All Blood Components

The following section is reproduced from the October 2017 Circular of Information (COI) for blood and blood components.

#### Immunologic complications

1. Hemolytic transfusion reaction, the destruction of red cells, is discussed in detail in the COI.
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 discussed in detail in the COI.
3. Febrile non-hemolytic reaction is typically manifested by a temperature elevation of  $\geq 1^{\circ}\text{C}$  or  $2^{\circ}\text{F}$  occurring during or shortly after a transfusion and in the absence of any other pyrexia stimulus. This may reflect the action of antibodies against white cells or the action of cytokines either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may 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 post-transfusion 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.
6. Transfusion-related acute lung injury (TRALI) is characterized by the acute onset of hypoxemia and non-cardiogenic 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 pro-inflammatory 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 anti-leukocyte antibodies, rare cases have implicated recipient anti-leukocyte antibodies that reacted with donor leukocytes. Widespread leukoreduction of blood components has likely mitigated this latter risk. Laboratory testing of blood donors for anti-leukocyte 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.
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 pre-transfusion testing. Alloimmunization to antigens of white cells, platelets, or plasma proteins can be detected only by specialized testing.
3. Post-transfusion 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.

## **Non-immunologic 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 section on testing of donor blood). 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 ( $\leq 1200$  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 ( $\geq 2^{\circ}\text{C}$  or  $\geq 3.5^{\circ}\text{F}$  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 water bath and red cell components stored for several weeks at 1 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 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 post-transfusion 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 hyperkalemia 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: 240-402-9160; efax 301-827-0333; e-mail: [fatalities2@fda.hhs.gov](mailto: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.

*Refer to the COI for references for this Appendix.*

## Appendix II

### Published Estimates of Transfusion Risks

The reported incidence of adverse reactions after transfusion varies widely among studies. Published rates depend on a number of factors, including but not limited to: the patient population and the presence of underlying disease, concurrent medication, or immunosuppression; blood component type and preparation method; and the surveillance methods used for reporting and characterizing transfusion reactions or suspected infections. Therefore, it is important to consider the many factors that affect the estimates of incidence in different clinical settings.

Before blood transfusion, the clinician should explain to the patient the potential risks, possible benefits and alternatives, when available, before transfusion. The Summary Table provides broad-based estimates from a variety of current sources which could be used to develop general information for patients. However, risk depends on patient-related factors, type and characteristics of the blood components, geographically defined and other variables which should be periodically evaluated, as warranted.

### Summary Table

Transfusion Reaction or Infection	Estimated rate among Transfused Patients
Allergic (mild)	1:20
Fever/chills (nonhemolytic)	1:50
Transfusion-associated circulatory overload (TACO)	1:100
TRALI	1:12,000
Acute hemolytic (mistransfusion)	1:40,000
Acute hemolytic (incompatible plasma)	1:50,000
Delayed hemolytic	1:50,000
Septic reaction (apheresis platelets)	1:100,000
Anaphylaxis	1:500,000
HIV, HBV, HCV	1:1,500,000-1:3,000,000

## Transfusion Reactions, Immediate

Description	Estimated Rate Among Transfused Patients	Comment	References
Acute hemolytic transfusion reaction (incompatible red cells)	1 per 12,000–38,000 Fatal: 1 per 600,000–1.5 million	About 2–7% of ABO-mistransfusion events are fatal	1-4
Acute hemolytic transfusion reactions (incompatible plasma)	1 per 46,000	Hemolysis is usually caused by Anti-A, and, less rarely, Anti-B, but ABO antibody titers are not predictive.	5, 6
Immune-mediated platelet destruction (refractoriness to platelet transfusion)	4–13%	About 50% of HLA-alloimmunized patients become refractory to prestorage leukoreduced components	7, 9
Febrile nonhemolytic reaction	<ul style="list-style-type: none"> <li>•RBC: 0.1-0.4%</li> <li>•Platelet concentrates: 0.1%</li> <li>•Apheresis platelets: 0.5-8%</li> <li>•PAS-C platelets (0.17%) vs. conventional apheresis platelets (0.5%)</li> </ul>	Prestorage leukoreduced cellular components	1, 2, 8, 10-12
Allergic reaction (mild)	<ul style="list-style-type: none"> <li>•RBC: 0.1-0.6%</li> <li>•Apheresis platelets: 1-5%</li> <li>•PAS-C platelets (0.3%) vs. conventional apheresis platelets (0.8%)</li> <li>•Plasma: 1-3%</li> </ul>	Prestorage leukoreduced cellular components	1, 2, 12, 13
Anaphylactoid/anaphylactic reactions	1 per 20,000–50,000 Fatal: 12 cases in 5 years	Most cases are idiosyncratic and a specific cause is not implicated. Rarely, reactions are associated with IgA deficiency or anti-IgA in patients. Passive transfer of blood donor hypersensitivity is a very rare cause of anaphylaxis in transfusion recipients.	1, 2, 13, 14
Transfusion-related acute lung injury (TRALI)	<p>Hospital-based surveillance:</p> <ul style="list-style-type: none"> <li>•1 per 12,000 plasma (male predominant) transfusions</li> <li>•1.4% of transfused adult noncardiac surgery patients</li> </ul> <p>Red Cross surveillance (per distributed units), 2015:</p> <ul style="list-style-type: none"> <li>•RBC: 1 per 480,000</li> <li>•Plasma (&gt;95% from male donors): 1 per 240,000</li> <li>•Apheresis platelets: 1 per 138,000</li> </ul>	Estimates depend on surveillance methods used by hospitals and blood centers	15-18
Transfusion-associated circulatory overload (TACO)	1–8%		1, 2, 19
Hypothermia	No published estimates—more likely to occur with massive transfusion or in pediatric and neonatal patients		
Metabolic complications (hypocalcemia, acidosis/alkalosis; hyper – or hypokalemia)	No published estimates—more likely to occur with massive transfusion or in pediatric and neonatal patients		
Septic reaction to bacterially-contaminated blood components	See Appendix 5A, Bacteria		

## Transfusion Reactions, Delayed

Description	Estimated incidence	References
Delayed hemolytic transfusion reaction	1 per 5,400–62,000 Fatal: 1 per 1.8 million	1, 2, 20
Alloimmunization (red cell antigens) (Delayed serologic transfusion reaction)	1 per 1,500–3,000 0.5% per RBC transfused	1, 2, 20, 21
Alloimmunization (human leukocyte antigens (HLA), human platelet antigens (HPA)) (prestorage leukoreduced components)	HLA: 10-17% of multiply-transfused patients HPA: 2-10% of multiply-transfused patients	7
Post-transfusion purpura (PTP)	Less than 1 per 2,000,000	20
Transfusion-associated graft-vs.-host disease (TA-GVHD)	Exceedingly rare; case reports with nonirradiated cellular components; 50% of cases occur in patients who do not have risk factors for developing TA-GVHD	1, 2, 22

## Appendix III

### Brief History of Infectious Disease Testing in the United States

Disease or Infection	Analyte	Year Introduced (or Modified)
Syphilis	<i>Treponema pallidum</i> antibodies	1950s
Hepatitis B	Hepatitis B surface antigen (HBsAg)	1971; 2006
	Anti-HBc	1986; 2006
	DNA	2008-2009
Hepatitis C	Anti-HCV	1990; 1992; 1997; 2011
	RNA	1999
HIV/AIDS	Anti-HIV-1/HIV-2	1985; 1992; 2009
	RNA	1999
HTLV	Anti-HTLV-I/II	1988; 1998; 2008
WNV	RNA	2003
Chagas'	<i>Trypanosoma cruzi</i> ( <i>T. cruzi</i> ) antibodies	2007 (universal) 2009 (selective, donor-based testing)
ZIKV	RNA (investigational)	2016 (June)-2018 (Dec)
	RNA (licensed)	2019 (Jan)
<i>Babesia microti</i>	<i>B. microti</i> antibodies and DNA (investigational) RNA only (investigational) RNA only (licensed)	2012 (June)-2018 (MA, CT, MN, WI) 2018 (May) (MA, CT, MN, WI) 2020 (May) (14 states + District of Columbia)

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; WNV, West Nile virus; ZIKV, Zika virus

## Appendix IV

### Routine American Red Cross Infectious Disease Test Methods (2021)

Infection	Marker	Assay Method	Trade Name
HBV	HBsAg (screen)	Chemiluminescent immunoassay (ChLIA)	Ortho VERSEIA
	HBsAg (confirmatory)	ChLIA, neutralization	Ortho VERSEIA
	Anti-HBc (screen)	ChLIA	Ortho VERSEIA
	HBV DNA (pooled screen)	Nucleic acid test (transcription mediated amplification; TMA)	Grifols/Hologic PROCLEIX Ultrio Plus (HIV-1/ HCV/HBV)
	HBV DNA (confirmatory if HBsAg and antibody screen nonreactive, and DNA screen nonreactive)	TMA as individual donation	Grifols PROCLEIX Ultrio Plus (HIV-1/ HCV/HBV)
HCV	Anti-HCV (pooled screen)	ChLIA	Ortho VERSEIA
	Anti-HCV (confirmatory)	Enzyme-linked immunoassay (EIA)	Ortho-Clinical Diagnostics HCV ELISA version 3.0, if RNA nonreactive
	HCV RNA (screen)	TMA	Grifols/Hologic PROCLEIX Ultrio Plus (HIV-1 /HCV/HBV)
	HCV RNA (confirmatory if antibody screen non-reactive, and DNA screen nonreactive)	TMA as individual donation	Grifols PROCLEIX Ultrio Plus (HIV-1 / HCV/HBV)
HIV-1, – 2	Anti-HIV-1/HIV-2 (HIV O Plus) (screen)	ChLIA	Ortho VERSEIA
	Anti-HIV-1/HIV-2 (confirmatory and differentiation)	GEENIUS HIV-1 /HIV-2 rapid test	Sanochemia HIV-1 IFA; Bio-Rad HIV-2 EIA and HIV-1/2 rapid test
	HIV RNA (pooled screen)	TMA	Grifols PROCLEIX Ultrio Plus Assay (HIV-1 /HCV/HBV)
HTLV I/II	Anti-HTLV-I/HTLV-II (screen)	ChLIA	Ortho VERSEIA
	Anti-HTLV-I/HTLV-II (confirmatory and differentiation)	western blot	MP Biomedicals, version 2.4 western blot
Syphilis	<i>Treponema pallidum</i> Antibody (screen)	Hemagglutination assay for IgG and IgM antibodies	Beckman Coulter, PK TP PK7300 System
	<i>Treponema pallidum</i> Antibody and Reagin (confirmatory)	ELISA and RPR	Trinity Biotech Captia-G ELISA and Becton Dickinson Macro-Vue RPR Card Test
WNV	WNV RNA (pooled screen)	TMA	Grifols/Hologic PROCLEIX WNV
	WNV RNA and Antibody (confirmatory)	TMA, PCR and IgM/IgG antibodies	Grifols PROCLEIX WNV; Roche PCR and Focus Diagnostics IgM/IgG
ZIKV	ZIKV RNA (pooled screen)	TMA	Grifols PROCLEIX Zika virus
	ZIKV RNA and Antibody (confirmatory)	TMA, and IgM/IgG antibodies	Grifols PROCLEIX Zika virus; Wadsworth IgM/IgG



Chagas	<i>T. cruzi</i> Antibody (screen)	ChLIA	Ortho VERSEIA
	<i>T. cruzi</i> Antibody (confirmatory)	Enzyme Strip Assay (ESA) and (EIA)	Ortho ESA and Ortho <i>T. cruzi</i> EIA
<i>Babesia</i>	<i>Babesia</i> RNA (pooled screen)	TMA	Grifols PROCLEIX <i>Babesia</i>
	<i>Babesia</i> RNA and Antibody (confirmation)	TMA, PCR and IgG antibodies	Grifols PROCLEIX <i>Babesia</i> , Roche PCR and in-house immunofluorescence assay
Bacteria (platelet components)	Bacteria	Bacterial growth in culture (aerobic and anaerobic media), 8-10mL each	bioMérieux BacT/ALERT 3D

## Appendix V – Transfusion-Transmitted Infections (TTIs)

### VA. Routine and Investigational Testing of Blood Donors

Agent	Prevalence in Blood Donations	Per Unit Residual Risk for Recipients	Time Period	Reference
HIV	1 per 60,606	1 per 2,941,176	2015-2016	23-26
HCV	1 per 8,718	1 per 3,333,333	2015-2016	23-26
HBV	1 per 17,094	1 per 1,470,588	2015-2016	23, 27, 28
HTLV-I/II	1 per 40,938	1 per 4,364,000	2007-2008	23
<i>Treponema pallidum</i>	1 per 4,054	No transmissions reported since 1960s	2007-2008	23, 29
WNV	1 per 109,890 – 192,308 (varies by year) during transmission season	15 cases of transfusion transmission from screened blood; 1 case from granulocytes identified after transfusion as positive; 1 case of transfusion transmission from plasma donation prior to triggering of ID-NAT in associated geographic region; 1 case of fatal TT-WNV from non-reactive apheresis platelet unit	June-Nov, 2014-2018	30-34
HEV	1 per 16,908	1 probable	2015-2016	62-66
<i>Trypanosoma cruzi</i>	1 per 15,544 (first-time donors/donations)	No transmissions reported from screened blood; 20 cases of transfusion transmission reported in non-endemic areas globally	2015	35, 36
Bacteria, Apheresis platelets	1 per 5,000	1 per 107,000 distributed components	2007-2012	37-42
Bacteria, WBD-pooled platelets (5 donors/pool)	1 per 1,200	ND	2007-2010	38

<i>Babesia microti</i> (as of December 2015) endemic in 9 states ME, NH, MA, CT, RI, NY, NJ, MN, WI)	1 per 390	1 per 18,000 in endemic areas; 165 potential TTB cases from 2010-2018; donors implicated in 90 transfusion transmissions	2012-2018 under IND in CT, MA, MN, and WI	43-46
Dengue virus (in Puerto Rico)	1 per 529 (2007); 1 per 573 (2012-2014)	0 transfusion transmissions from screened blood; 2 clusters of transfusion transmissions from unscreened blood in Puerto Rico	2012-2014 under IND in Puerto Rico	47, 48
Zika virus: Please see Appendix VI	—	—	—	

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

## VB. Donor Screening Tests Not Routinely Used or Not Available

Transfusion-Transmitted Infection	Estimated Incidence, Transfusion-Transmitted Infection	Reference
Cytomegalovirus	1-4% with CMV reduced-risk components (seronegative donor or leukoreduced component)	49
Malaria ( <i>Plasmodia spp.</i> )	RBC: <0.1 per 10 <sup>6</sup>	50-52
Leishmaniasis ( <i>Leishmania spp.</i> )	Rare case reports	53
vCJD	4 cases worldwide	54-56
CJD	None	57, 58
Lyme disease ( <i>Borrelia burgdorferi</i> )	None	59
Bacteria	Red cells: 1 per 5,000,000 (Platelets: see Appendix 5A)	60
Chikungunya virus (in Puerto Rico)	Frequency in blood donors in Puerto Rico, 0.54%; No documented transfusion transmission	61
Hepatitis E virus	HEV-RNA prevalence in the US 1 per 16,908. Cases of transfusion transmission documented but rarely causes acute morbidity	62-66

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## Appendix VI: Zika Virus

Zika virus is a mosquito-borne flavivirus closely related to dengue viruses and was responsible for a large outbreak in the Americas first documented in Brazil in May 2015<sup>(1)</sup>. Zika virus has been proven to cause fetal loss, congenital Zika virus-related syndrome including microcephaly, Guillain Barré syndrome and other neurological complications in adults<sup>(1-7)</sup>. However, in most cases (~80%) Zika virus infection is asymptomatic.

Zika viral RNA can be recovered from blood donors, as first demonstrated in the 2013-2014 Zika virus outbreak in French Polynesia in which approximately 2.8% of donors tested RNA positive by nucleic acid testing (NAT)<sup>(8)</sup>. To date, there have been four probable transfusion transmissions, all reported in Brazil<sup>(9,10)</sup>. These occurred from three donors who were identified by post-donation information reports of dengue/Zika virus-like symptoms. None of the recipients developed Zika-related symptoms following transfusion. In addition to mosquito-borne transmission and likely transfusion transmission, sexual transmission has also been documented with 36 cases reported<sup>(1,11)</sup>. Although the majority of sexually transmitted Zika virus cases have been from an infected male to his partner (male or female), a suspected case of female to male sexual transmission has also been reported by the United States Centers for Disease Control and Prevention (CDC)<sup>(12)</sup>.

The duration of Zika plasma viremia is believed to be 1-2 weeks, consistent with other mosquito-borne viruses. Viral clearance has been estimated to be 19 days for 95 percent of affected patients (95% confidence interval of 13-80 days in a pooled analysis of published studies)<sup>(13)</sup>. However, Zika virus has been shown to persist longer in whole blood, semen and urine versus serum and plasma. One report found persistence of Zika viral RNA in whole blood for 101 days post-symptom onset despite RNA-negative findings in corresponding serum samples; RNA positivity for 14, 21 and 63 days occurred in urine, saliva and ejaculate from the same patient, with intermittent detection on days 56, 49 and 77 in the same biological fluids, respectively<sup>(14)</sup>. Based on a study documenting that 5 days after symptom onset, 82% of Zika virus clinical cases remained RNA positive from urine but not serum, urine is now recommended by the CDC as a preferred sample type in patients with suspected Zika virus disease<sup>(15)</sup>. In pregnant women with clinical symptoms compatible with Zika virus infection, both urine and serum testing should be performed in specimens collected as soon as possible within 12 weeks of symptom onset<sup>(16)</sup>. The longest persistence of Zika virus has been shown in semen. In one case, RNA was detected for 93 days and in another for 188 days, both from returning travelers to Zika active or previously active areas<sup>(17,18)</sup>. The number of Zika travel-associated, sexually transmitted and mosquito-borne cases in the mainland US and its territories continues to be updated. Refer to the CDC website for updates (<https://www.cdc.gov/zika/reporting/index.html>).

Cases continue to decline with no local transmissions of Zika virus reported in the continental US in 2018-2019; reported case decreases are noted below:

- In 2019, there were 19 total cases, all but 1 related to travel to ZIKV-active areas outside of the US, and 1 lab-related case;
- In 2018, there were 74 total cases with all but 1 related to ZIKV travel and 1 lab-related case;
- In 2017, there were 452 total cases of which 2 occurred in S Florida and 5 in S Texas (Brownsville);
- In 2016, there were 5168 total cases of which 218 occurred in S Florida and 6 in S Texas (Brownsville).

Because of concern about severe disease associations, rapid virus spread in the Americas, recovery of RNA from blood of asymptomatic donors, and reports of transfusion transmission, blood centers were required to screen for the presence of Zika virus RNA in blood and follow the current requirements for donor deferral as provided by FDA Guidance released on July 6, 2018 (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/revised-recommendations-reducing-risk-zika-virus-transmission-blood-and-blood-components>) .

Investigational blood donation screening by NAT under FDA-allowed investigational new drug (IND) applications was initiated on April 4, 2016, with testing in Puerto Rico, an area of active Zika virus transmission at the time. Rates of positivity exceeded 1% in Puerto Rico during the outbreak<sup>(19)</sup>. Two NAT assays were allowed for use under INDs. Both are now FDA licensed: one manufactured by Roche Molecular Systems and the other by Grifols. The Red Cross began investigational testing using the Grifols assay in several southern States on June 20, 2016. On July 5, 2018, the FDA licensed the Procleix Zika Virus Assay (Grifols' transcription mediated amplification, TMA) and a day later released industry guidance "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components" that states blood establishments must use a licensed donor screening test for ZIKV using either minipool (MP-) or individual donation-nucleic acid testing (ID-NAT). If MP-NAT was used, establishments must also develop a strategy to convert to ID-NAT if triggered. The Red Cross developed new processes and procedures to support the conversion from unlicensed to licensed ZIKV testing, including the development of a triggering strategy (same as for WNV), and transitioned to licensed ZIKV test on November 26, 2018. ID-NAT continued until December 31, 2018 and transitioned to MP-NAT on January 1, 2019.

During the IND clinical study, from June 20, 2016 to December 17, 2018, the Red Cross tested a total of 10,492,683 donations, of which 393,713 donations were tested by MP-NAT and 10,098,970 were ID-NAT tested. No reactive donations were identified by MP-NAT. A total of 11 (2.6%) confirmed-positives (CP) of 430 initially-reactive donations were identified for a confirmed-positive rate of 1:953,880; a positive predictive value of 2.6%; and specificity of 99.996%. Confirmatory testing included repeat TMA, RT-PCR (alternate NAT), serology and RBC TMA.

Of the 11 CP donations, 7 (64%) were ID-NAT repeat reactive of which 5 were PCR positive or equivocal and IgM negative (i.e., window-period donations). Confirmed-positive index donations were tested by TMA in simulated pools of 16 samples that were run in triplicate. Pool testing was 100% reactive for all window-period donations. ZIKV RNA was detected in RBCs from confirmed-positive index donations with estimated levels varying from 40 or fewer copies/mL to 800,000 copies/mL (vs RNA levels in plasma ranging from 12 or fewer to 1,000,000 copies/mL). Confirmed-positive donors resided in Texas, California, New York, Washington, West Virginia, 2 in Massachusetts and 4 in Florida, 2 of which were local transmissions, one of which also involved a sexual partner. Eight donors had traveled to a ZIKV-active area returning to the US from 2 to 75 days prior to donation (average 33.3 days) (November 2, 2016 to March 16, 2018 donations) (Table). Two donors with a travel risk reported clinical symptoms while 9 remained asymptomatic, for a ratio of symptomatic/asymptomatic ZIKV-confirmed-positive donors of 18%/82%, consistent with previous reports. Four of the 5 window-period donors seroconverted at days 6, 7, 8 and 17 of follow-up (average 9.5 days). The fifth window-period donor was the recipient of an experimental ZIKV vaccine (ZIKV purified inactivated vaccine, ZPIV); this donor provided 3 additional samples at 14, 23 and 38 days; none were ZIKV-IgM positive (the donor was TMA-RR and alternate NAT equivocal at index). The longest period of ZIKV-RNA detection in RBCs in our study was 154 days vs 66 days in plasma from the same TMA-RR donor. ZIKV IgM detection persisted in all seropositive donors for the duration of the follow-up study (range 4 to 225 days, average 105 days). Earlier sets of data were presented at the AABB Annual Meeting in October 2017 and published in the New England Journal of Medicine on May 10th, 2018<sup>(20)</sup>.

**Table. State of residence and travel-risk of ZIKV-confirmed positive donors**

Confirmed positives	Collect Date	Donor Residential State	Travel to a ZIKV active area
1	11/02/16	Texas	Puerto Rico
2	11/18/16	California	St. Maarten
3	12/05/16	Florida	Local Transmission
4	12/27/16	Massachusetts	St. Thomas
5	01/10/17	Florida	Curaçao
6	01/12/17	Florida	Local Transmission
7	01/31/17	New York	St. Kitts and Nevis
8	03/13/17	West Virginia	Aruba
9	05/16/17	Massachusetts	Vaccinee
10	12/28/17	Washington	Mexico
11	03/16/18	Florida	Cuba

Between December 17, 2018, the end of the IND, and December 31, 2019 an additional 4,790,616 donations were screened for ZIKV of which 182,661 were tested by ID-NAT and 4,607,955 in minipools. Nine reactive donations were identified, 7 by ID-NAT and 2 by MP-NAT but none confirmed positive; none resulted in a triggering event. Overall, considering all testing done at the Red Cross since ZIKV-screening was implemented on June 20, 2016, the confirmed-positive rate of ZIKV infection among blood donors is 1:1,389,391; for an overall specificity of the Procleix Zika Virus Assay of 99.997% and a positive predictive value of 2.5%.

Previous cost estimates of ZIKV-screening at the Red Cross were \$5.3 million per ZIKV-positive donation during 2016-2017 (8 identified from >4 million screened) or a total of \$42 million over 15 months<sup>(20)</sup>, and a total annual cost estimate of \$137 million<sup>(21)</sup>. An analysis of the cost effectiveness of ZIKV testing was published with collaborators<sup>(22)</sup>. This article demonstrates that no strategy for testing within the 50 US states is cost effective with an ID-NAT cost of \$341 million per QALY.

The FDA licensed pathogen reduction process for platelets and plasma (Intercept, Cerus Corp) has been shown to be effective for arboviruses. Published data demonstrate a > 6 log<sub>10</sub> reduction in Zika virus infectivity titers in plasma<sup>(23)</sup> with similar



reductions observed for apheresis platelets<sup>(24)</sup>. Testing a plasma repository collected in Puerto Rico from February 2015 to May 2016 as part of Cerus' "TRUE" clinical trial, with the goal of determining the effectiveness of pathogen reduction in preventing the transfusion transmission of arboviral infections, identified the first Zika virus RNA positive blood donor in Puerto Rico. The donor was collected in December 2015, coincident and related to the first reported autochthonous cases of Zika virus in the island. Molecular analysis of the Zika virus strain recovered from the donor confirmed its relatedness to the Puerto Rican lineage and identified the estimated time of Zika virus introduction to the island to be approximately 4.5 months prior to the confirmed-positive donation<sup>(25)</sup>. Routine donation screening didn't start in Puerto Rico until April 4, 2016 (as noted above).

Due to the absence of on-going outbreak activity worldwide and no activity in the US, it is possible that Zika virus RNA screening may be deemed unnecessary.

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