

### **RED BLOOD CELLS ordering terminology:**

In emergency situations, with a Physician's signature, usually on the back of the Request Form, **group O Rh negative uncrossmatched** RBCs can be released immediately. In urgent situations, with a Physician's signature, **ABO/Rh group specific uncrossmatched** RBCs can be released within 10 minutes.

Blood Banks request that unused group O Rh negative units be returned as soon as possible when **Type and Crossmatch** blood becomes available.

On rare occasions, Blood Bank inventory of Rh negative RBCs may become critically depleted. On these occasions, in emergency and/or urgent situations, the Blood Bank Pathologist may order the substitution of Group O Rh positive RBCs for Rh negative males or females 45 years or older.

A Stat order for **Type and Crossmatch** RBCs can be completed within one hour unless alloantibodies are found, which require additional time for completion of pre-transfusion testing. If autoantibodies are found, crossmatch compatibility testing must exclude an underlying, or hidden, alloantibody. A Priority order for **Type and Crossmatch** RBCs can be ready in 4 hours or less, and a Routine order can be ready within 8 hours, unless alloantibodies are found.

**Type and Crossmatch** orders include ABO/Rh typing of the patient, testing for antibodies to common red cell antigens, and crossmatch with RBC unit(s) in the Blood Bank inventory. Each crossmatched RBC unit in inventory is reserved for that patient, and thus is **unavailable** for transfusion of other patients.

If no prior arrangement is made with the Blood Bank, most Type and Crossmatch orders expire at 48 hours, and a new blood sample for Type and Crossmatch testing is required. With few exceptions, crossmatched RBC units are released to the Blood Bank general inventory after 48 hours; however, some hospitals allow crossmatched RBC units to be reserved an additional 24 hours by notifying the Blood Bank.

**Type and Screen** orders include ABO/Rh typing of the patient and testing for antibodies to common red cell antigens. If the Type and Screen has been performed and the antibody screen is negative, crossmatch-compatible RBCs can be **provided from Blood Bank inventory for the patient within minutes, without additional blood sample**. For those invasive procedures with a low probability of requiring blood transfusion, Blood Banks ask that **Type and Screen** orders be written, so that RBC units in inventory will not be removed from availability for other patients. Most Type and Screen orders expire after 48 hours.

In cases where the patient's pre-transfusion serum sample demonstrates a warm autoantibody [i.e. patient's RBCs have a positive direct antihuman globulin test (DAT)], crossmatch compatibility testing may take hours or days, in order to exclude an underlying, or hidden, alloantibody. If the clinical situation precludes waiting for the completion of pre-transfusion testing, then with a Physician's

signature, the Blood Bank will release the “least incompatible” blood, based on what history and testing have been able to ascertain and determine. In these cases, it is recommended that the “least incompatible” RBCs be used as sparingly as possible, only for preventing hypoxemic damage to vital organs, until the standard pre-transfusion testing can be completed. Due to the greater risk for hemolysis of transfused “least incompatible” RBCs, close monitoring is necessary during these transfusions.

If indicated, Special Attributes (leukoreduced, CMV negative, irradiated, volume reduced, or washed RBCs) may also be requested (See **Special Attributes**). A Blood Bank Pathologist must be on-call at all times, and can be reached through the Blood Bank.

**RED BLOOD CELLS definitions:** One unit of packed red blood cells (RBCs) consists of erythrocytes concentrated by centrifugation from a single unit of whole blood donation or collected by apheresis, along with added sodium citrate (anticoagulant) and preservative. A unit of packed CPD RBCs has a volume of 300 to 350 mL and retains approximately 50 mL of donor plasma, and also CPD (citrate anticoagulant, phosphate buffer, and dextrose as preservative). More routinely, adenine and NaCl (AS-3 RBCs), and also mannitol (AS-1 RBCs), are included as preservatives.

Adult patients are routinely given units of AS-1 or AS-3 RBCs, with an approximate hematocrit of 55 to 65%. Infants, 4 months or less, are given ‘fresh’ CPD RBCs, with approximate hematocrit of 70 to 80%, which are “fresh”, less than 6 days since collection. Additionally, only hemoglobin S negative (sickle trait negative) blood is dispensed for preterm infants, for neonatal exchange transfusion, and for infants receiving multiple transfusions from the same RBC unit. The hematocrit of all units of packed RBCs is always less than 80%.

RBCs contain approximately 200 to 250 mg of iron, or 50 to 60 grams hemoglobin; and if less, the unit is designated by the Blood Bank as “low volume collection”. RBCs are stored at 1° to 6° C, with CPD units outdating at 21 days, and AS-1 and AS-3 units outdating at 42 days. RBCs contain nonfunctional leukocytes and platelets.

HLA class 1 antigens are only minimally expressed on mature RBCs; however, units of RBCs contain ‘passenger’ lymphocytes, so consideration of the patient’s clinical status may warrant transfusion of leukoreduced RBCs in order to reduce the risk of HLA sensitization, especially for those patients with a significant likelihood of needing future organ transplantation.

Please note that NO unused RBCs can be returned to inventory if they have been out of the Blood Bank for more than 30 minutes, unless the RBCs have been kept in Blood Bank approved controlled cool storage.

**RED BLOOD CELLS dosages and indications:** In an average adult, one unit of RBCs can be expected to raise hemoglobin (Hgb) by 1 gm/dL (Hct by 3%). In pediatric patients, 5 to 10 mL/Kg dosage of AS-1 or AS-3 RBCs can

increase hemoglobin (Hgb) by 1 gm/dL. For neonates, the same 5 to 10 mL/Kg dosage increases Hgb slightly more when 'fresh' (6 days or less since collection) CPD RBCs are given, due to the higher Hct of CPD RBCs. The half-life of transfused RBCs is approximately 30 to 40 days.

RBCs are only compatible for infusion with normal (0.9%) saline solution, ABO compatible plasma, or 5% albumin. Do not transfuse with Ringer's lactate solution because it contains enough Calcium ion to inactivate the citrate anticoagulant. Drugs or medicines must NOT be infused via the same intravenous line during transfusion. RBCs must be transfused through a 180 to 260 micron blood administration filter. Transfusion of each unit of RBCs must be completed within 4 hours. Patients with cold agglutinins (cold autoantibodies) may need transfusion through a blood warmer to protect the transfused cells from hemolysis.

RBCs are indicated when active bleeding approaches or exceeds 20% of blood volume, and can be replaced to keep pace with loss. In these cases, there has often not been time for compensatory expansion of plasma volume, so the Hematocrit (Hct) does not accurately reflect the RBC loss, and clinical findings such as hypotension, tachycardia, etc. are more reliable. There are "recipes" to maintain equilibration of blood components transfused during resuscitation; for example, giving 4 units of Plasma and 6 Random Donor Platelet units (1 Single Donor pheresis pack) for every 8 units of RBCs; and 10 units of Cryoprecipitate for every 16 units of RBCs. No "recipe" is ideal for every situation.

Many hospitals have Massive Transfusion Protocols (MTP's) for severely injured patients, and these protocols often recommend greater reliance on plasma than on crystalloid solutions during resuscitation, with ratios of RBCs to Plasma of 2:1 or even 1:1 during emergency resuscitation (Transfusion, 2011; 51: 1925-1932). These Protocols provide more rapid replacement of coagulation factors, and patients often require fewer blood components for resuscitation, with less frequent resort to supplementary recombinant activated Factor VII (rVIIa). RBC cytoplasmic 2,3-DPG decreases during storage to low levels by 14 days, shifting the RBC hemoglobin oxygen dissociation curve to the left. Recovery of normal cytoplasmic 2,3-DPG occurs over several hours following transfusion. For this reason, some trauma surgeons are requesting 'fresh' (6 days or less since collection) RBCs be part of Massive Transfusion Protocols. Ongoing scientific studies have not yet corroborated improved outcomes with this modification, so hospital Blood Banks must make this consideration in correlation with Blood Bank inventory and anticipated needs of the hospital.

Hematocrit (Hct) thresholds for transfusion are suggested for certain pre-existing conditions. In anemia, whether due to hemolysis, chronic blood loss, or marrow insufficiency, when  $Hct \leq 20\%$ , RBC transfusion may reduce tissue hypoxia. For patients with invasive intensive monitoring, the oxygen extraction ratio may be directly measured by subtraction of the central venous blood oxygen saturation ( $S_{vO_2}$  = normally about 75%) from the arterial blood saturation ( $S_{aO_2}$  = normally about 100%), and an oxygen extraction ratio of greater than 0.5 (50%) is considered to be a critical value. Indeed, if pulmonary function and cardiac output are adequate, so that  $S_{aO_2}$  may be assumed to be 100%, than an  $S_{vO_2}$

less than 60% is an indication of tissue hypoxia. An oxygen extraction ratio of 0.5 or higher confirms clinical need for increased oxygen-carrying capacity by RBC transfusion.

Higher Hematocrit (Hct) thresholds for transfusion are suggested if there is also associated cardiorespiratory impairment, such as Hct  $\leq$  24% if coronary artery disease (CAD), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), or peripheral arterial disease (PAD); or Hct  $\leq$  30% if acute myocardial infarction (MI); or Hct  $\leq$  36% if ventilator dependent; however, transfusion to much higher than Hct 30% lowers survival of elderly patients with acute MI (N.E.J.M., 2001; 17: 1230-1236). Maintenance of higher Hct threshold is suggested (Hct  $\leq$  20%) for some hemoglobinopathies, eg. SS disease, to suppress endogenous production. RBCs combined with appropriate corresponding transfusions of Platelets, Plasma, and Cryoprecipitate are indicated for exchange transfusions, i.e. for hemolytic disease of the newborn, or for patients with sickle cell disease in crisis or having acute chest syndrome or having major surgery.

The cardiorespiratory status must be considered in deciding the rate, as well as the amount, of transfusion, in order to avoid circulatory volume overload. In chronic anemia, however, the blood volume is only slightly decreased due to the compensatory expansion of plasma volume, so rapid or excessive transfusion carries increased risk of hypervolemia and circulatory overload.

Patients with certain types of chronic anemia, with an expectation of receiving large numbers of RBC units over their lifetimes, such as the thalassemias, sickle cell disease, pure red cell aplasia (Diamond-Blackfan), aplastic anemia, etc. will tend to become sensitized to minor blood group antigens over time, which will make it more difficult to obtain cross-match compatible RBCs from the routine Blood Bank inventory in times of need. This tendency can be retarded by requesting various degrees of phenotypic matching for high incidence, clinically significant RBC minor blood group antigens for routine/regularly scheduled transfusions. Blood Bank consultation helps treatment planning of transfusion-dependent patients.

**RED BLOOD CELLS contraindications and hazards:** Acute hemorrhage less than 20% of blood volume should be resuscitated with crystalloid (electrolyte) and/or colloid [albumin or plasma protein fraction (e.g. Plasminate)] solutions. Nutritional anemia should be treated nutritionally. Marrow insufficiency should be treated with erythropoietin.

Hazards of RBC transfusion can be either acute (immediate) or delayed, and can be classified as due to immune or non-immune mechanisms.

Acute hemolytic transfusion reaction (AHTR) is caused by the acute immune-mediated destruction of transfused RBCs, due to alloantibodies directed against ABO, Rh, Kell, or other RBC antigen(s). The most common cause of acute hemolytic transfusion reaction is clerical error in the patient identification, either at the time of ordering or of phlebotomy for the Type and Crossmatch, or at

the time of intravenous infusion. Acute hemolytic transfusion reaction becomes apparent during or shortly after transfusion, and may present with any mixture of the following clinical signs: fever, chills, flushing, nausea or vomiting, chest or flank pain, dyspnea, hypotension, tachycardia, shock, bleeding or disseminated intravascular coagulation (DIC), hemoglobinemia or hemoglobinuria, oliguria or anuria. In anesthetized patients, hemolysis (hemoglobinemia, hemoglobinuria), hypotension and/or increased bleeding (oozing) in the operative field due to DIC/coagulopathy may be initial signs of AHTR (See **Transfusion Reactions**).

For both immediate and delayed hemolytic transfusion reactions, usually the direct antihuman globulin test (DAT) will be positive with immune-mediated RBC destruction; however, if immune destruction of transfused RBCs has been complete, then the DAT result may be deceptively negative. A positive DAT can also be present in patients with autoimmune hemolytic anemia or drug-dependent autoimmune hemolytic anemia (i.e. penicillin), in recently transfused patients (within 3 months), or nonspecifically with some medications or collagen diseases. Hemoglobinemia (recognizable as pink/red plasma following centrifugation), hemoglobinuria, and decreased haptoglobin are other laboratory findings seen with acute hemoysis.

Some diseases that may simulate hemolytic transfusion reactions include autoimmune hemolytic anemia, drug-dependent autoimmune anemia, some RBC membrane defects, paroxysmal nocturnal hemoglobinuria (PNH), some enzyme deficiencies (eg. G-6-PD deficiency), some hemoglobinopathies, and malignant hyperthermia.

Acute immune-mediated transfusion reactions due to the plasma within each unit of RBCs include transfusion-related acute lung injury (TRALI or noncardiogenic pulmonary edema), as well as allergic (i.e. urticarial) transfusion reactions, and also anaphylactic/anaphylactoid transfusion reactions. Febrile nonhemolytic transfusion reactions (FNHTR) are due to cytokines produced by 'passenger' white blood cells in RBC units (see **Plasma** and see **Transfusion Reactions**).

Acute, but non-immune, RBC transfusion reactions include transfusion-associated circulatory overload (TACO). Much less commonly, transfusion of damaged RBCs or bacterially contaminated RBCs may cause life-threatening reactions (see **Transfusion Reactions**). Improper use or malfunction of blood warming devices can cause severe hemolysis of the RBCs being transfused.

Delayed hemolytic transfusion reactions (DHTR) are due to latent, or anamnestic, immune responses directed against transfused RBCs. DHTR may present days to weeks after transfusion with any combination of fever, anemia, and/or mild jaundice. Post-transfusion purpura (PTP) is an uncommon delayed transfusion reaction, presenting as thrombocytopenia, due to autoimmune hypersensitization incited by 'passenger' platelets in RBC units, against the transfusion recipient's own platelets.

RBC alloimmunization is the development of an antibody against one or more of the RBC antigens present on transfused RBCs. The development of a new alloantibody usually takes weeks to months, and the levels of the antibody may remain high for the recipient's lifetime, or they may diminish and become

latent over time. Sometimes latent alloantibodies are not able to be detected by the Blood Bank during the initial Typing and Crossmatch testing; but re-exposure to the antigen by RBC transfusion elicits an anamnestic immune response, with production of high levels of the alloantibody within a few days.

Transfusion Associated-Graft versus Host Disease (TA-GVHD) is a rapidly fatal disease caused by the engraftment of 'passenger' T lymphocytes in the RBC unit, which may occur in some immunocompromised recipients, in some lymphoma patients (especially Hodgkin's disease) or, less frequently, in a closely-matched HLA recipient (eg. a "blood relative"). TA-GVHD is prevented by irradiation of the RBCs by the Blood Bank prior to transfusion, preventing the proliferation of all transfused 'passenger' lymphocytes (see **Special Attributes**).

Iron overload (hemosiderosis) is a non-immune delayed adverse reaction due to multiple transfusions, generally in patients who have congenital hemolytic anemia, some hemoglobinopathies, pure red cell aplasia, aplastic anemia, or chronic renal failure. Patients at risk for transfusion-related iron overload must receive chelation prophylaxis in order to prevent damage to heart, liver, and/or endocrine organs.

Donor selection and product testing have made RBCs very safe, but the very rare risk of transmission of infectious agents of disease must always be considered when ordering RBCs for transfusion (see **Infection Risks**).