Transfusion Triggers

In the United States nearly 15 million units of whole blood are processed annually with ~13 million patients receiving blood component transfusions. Due to increasing demand and an ever-dwindling supply, appropriate blood may not always be available when needed. In addition, risks such as transfusion-transmitted diseases and adverse reactions to blood components are still a viable threat to patient safety despite the implementation of advanced donor testing methodologies. Thus, in order to minimize risk and maximize blood product availability, a review of appropriate transfusion triggers, or guidelines, is warranted. This article is intended to briefly review the most commonly used blood products, their evidence-based indications, and appropriate dosages.

RED CELL TRANSFUSION THERAPY:

Although there are many underlying clinical reasons, the primary impetus for red blood cell (RBC) transfusion should be to increase oxygen delivery to tissues. Many RBC transfusions occur in the acute setting. It is generally accepted that blood loss less than 20-30% of total blood volume can be corrected with crystalloid or colloid solutions to maintain intravascular volume. Losses of >30% often require RBC transfusion as the loss of oxygen carrying capacity could acutely overwhelm any compensatory measures and result in hypovolemic shock.

There is ongoing debate as to the optimal transfusion trigger for RBCs. Because patients have inherent differences with regard to cardiac compensation and tolerance of anemia, a universal transfusion trigger is inappropriate. Induction of normovolemic anemia in normal, healthy subjects has shown that a hemoglobin level of 6 g/dL is generally well-tolerated due primarily to cardiac compensation. Numerous studies have concluded that unnecessary transfusions are avoided if 7 g/dL is used as a transfusion trigger in hospitalized patients, though this is increased to 9.5-10.0 g/dL in patients with a history of cardiovascular disease. Stable patients with anemia due to nutritional deficiency do not require RBC transfusion and should be treated with appropriate supplements. Studies have shown that such restrictive triggers are associated with reduced morbidity and mortality.

After determining that a patient qualifies for RBC transfusion, it is also important to determine an appropriate RBC dose. The current standard RBC unit contains an additive (preservative) solution with a final volume of approximately 300-350 mL. For these units, hematocrits range from 55-60%, much lower than the “packed” units used many years ago which had hematocrits >75%. For the anemic, non-bleeding adult patient, one unit of RBCs should raise hemoglobin by approximately 1 g/dL (and hematocrit by approximately 3%). In the non-bleeding pediatric patient, a RBC dose of 10-15 mL/kg may raise the hemoglobin by upwards of 2-3 g/dL (equivalent to a 6-9% increase in hematocrit).

PLATELET TRANSFUSION THERAPY:

A current topic of debate is whether to provide prophylactic platelet (PLT) transfusions to chronically thrombocytopenic patients. And if so, what is an appropriate PLT count trigger? Ongoing trials are underway to determine if prophylactic PLT transfusion is superior to a policy of withholding transfusion until an active bleed has begun to occur.

Based on available evidence, the best current practice suggests provision of prophylactic PLT transfusions to avoid active bleeds since PLT-related bleeding can be severe, life-threatening, and difficult to acutely manage. Two important transfusion studies clearly showed that significant, spontaneous bleeding does not occur until the platelet count is ≤10,000 /uL. This guideline has proven to work well for non-bleeding adult patients and is particularly relevant for populations with oncologic and hematologic disorders. Higher “prophylactic” PLT counts may be sought for neonatal and pediatric populations; no clear guidelines currently exist for these groups. For actively bleeding patients, like those involved in trauma or for patients undergoing major invasive surgical procedures, more aggressive care and a higher transfusion trigger are warranted. Studies have shown that most major invasive procedures can be performed with PLT counts >50,000/uL. Of note, patients with neurological or ophthalmologic hemorrhage, or those undergoing major invasive procedures in these two anatomical locations, may
require PLT counts >100,000/uL. Yet another consideration is the bleeding patient on anti-PLT therapy such as aspirin or clopidogrel. For these patients, PLT counts are likely to be entirely normal and ultimately irrelevant as a large percentage of PLTs are non-functioning. As such, PLT transfusion for significant bleeding may be warranted for any patient on anti-PLT therapy regardless of underlying counts.

PLTs are issued from the blood bank in one of two forms: single donor PLTs collected by apheresis or random donor pooled PLTs (consisting of a pool of individual units from 5 separate donors). In general, 1 random donor pool of 5 units or 1 single donor unit should raise PLT counts by 40-50,000/uL in adults. Doses of 5-10 mL/kg should result in a PLT increase of 50-100,000/uL for children. Thus, one PLT transfusion should initially be sufficient to address most PLT-related bleeding issues for patients with low PLT counts, those on anti-PLT therapies, or for those undergoing invasive procedures. Only rarely will the blood bank simultaneously issue two pools or two single donor units for an adult patient. Such cases are generally restricted to those where PLT counts of >100,000/uL are absolutely required. In such a scenario, or for patients not appearing to have an incremental increase in PLT counts following routine transfusion, consultation with a Transfusion Medicine physician is strongly suggested to help develop a plan of action.

PLASMA TRANSFUSION THERAPY:

Plasma is the acellular portion of blood that is either separated by centrifugation from whole blood donations or collected directly by apheresis. Plasma contains physiologic levels of all elements of the coagulation cascade. Thus, plasma is most frequently used to temporarily replenish deficient coagulation factors (e.g. in liver disease, DIC, or massive transfusion) and for the urgent reversal of warfarin. Less frequently, plasma is used as a replacement product in plasma exchange therapy as for patients with thrombotic thrombocytopenic purpura (TTP).

Plasma Transfusion in the Non-Bleeding Patient

For the non-bleeding patient with a prolonged INR (generally >1.5), most guidelines recommend against the initial use of FFP. This is particularly true for patients with prolongation of INR due to the administration of vitamin K antagonists or vitamin K deficiency. In their guidelines, the American College of Chest Physicians recommends that for the non-bleeding patient with an INR less than 5.0, simply holding or adjusting anticoagulant dosing is appropriate (Ansell J et al, 2008). For patients with INRs of 5.0-9.0 and no evidence of bleeding, the guidelines suggest omitting doses of vitamin K antagonists with subsequent administration of oral vitamin K to those patients at the greatest risk for hemorrhage. Even patients with INRs > 9.0 do not necessarily require plasma transfusion therapy. In these cases, anticoagulant medications should be stopped and vitamin K more aggressively replenished via the oral or intravenous route. For patients with vitamin K deficiency due to some other reason (e.g. a nutritional deficiency), administration of vitamin K at any INR > 1.5 would be appropriate, particularly if the patient is at risk for bleeding. Unfortunately, there are no clear guidelines on the use of plasma transfusion for patients incapable of responding to vitamin K dosing (e.g. severe liver disease) or for those with congenital factor deficiencies. For such patients, decisions on plasma transfusion (or administration of factor concentrates if available) must be made on a case-by-case basis in accordance with the risk for the development of a significant bleed.

Plasma Transfusion in the Bleeding or Pre-Operative Patient

For the bleeding patient with a prolonged INR (generally >1.5) due to any cause, the infusion of fresh frozen plasma (FFP) is appropriate. In the pre-operative patient with a prolonged INR, use of FFP should be minimized whenever possible. For instance, a patient on warfarin undergoing elective surgery may be managed simply by holding anticoagulant doses in the days preceding surgery. In these cases FFP therapy should be implemented only when such an approach fails to adequately correct the INR.

Dosing of FFP in the bleeding or peri-operative patient is geared toward attaining at least 30% plasma factor activity in the recipient since such levels are sufficient for normal clotting. It is important to note that FFP should not be dosed in proportion to the prolongation of a patient’s INR (i.e. the higher the INR, the more units of FFP needed). Rather, FFP is most appropriately dosed according to the weight of the recipient. The YNHH Blood Bank recommends plasma dosing at 10-15 mL/kg recipient weight. Such doses should adequately replace >30% of coagulation factors and correct coagulation studies independent of the baseline INR in the majority of patients. Since most single FFP units are 200-250 mL, 2-4 units of FFP should be sufficient to treat the 60-90kg adult. A similar weight-based dose (10-15 mL/kg) can be applied to pediatric patients to achieve replacement of coagulation factors. Routine coagulation testing to gauge the efficacy of FFP and the need for future transfusions is also recommended.

Unlike some other blood products, the timing of plasma transfusions in relation to an invasive procedure is particularly important due to the short circulating half-lives of many plasma clotting factors. As such it is recommended that plasma be transfused as closely as possible to the time of the planned intervention. For instance, if a patient with an INR of 2.5 is going for surgery, FFP to reverse the INR should be infused within 30-45 minutes of the start of the procedure. Infusion of plasma hours (or even days!) before a surgery will only result in immediate
consumption of transfused factors and a return to the patient’s baseline INR within 4-5 hours of the transfusion. Such a transfusion strategy provides little patient benefit. Since FFP results in only a temporary correction of coagulopathy, patients who qualify for FFP infusion should also have their anticoagulant dosing held and/or receive vitamin K as clinically appropriate. Such strategies will allow for a more prolonged correction of coagulopathy in the bleeding patient.

CRYOPRECIPITATE THERAPY:

Cryoprecipitate, or “Cryo” as it is often called, is prepared by thawing one unit of fresh frozen plasma (FFP) in the cold between 1-6ºC, removing the supernatant plasma, and re-freezing the cold insoluble precipitate. Like PLTs, most doses of Cryo are pooled for adult patients since individual units are typically of small volume (generally 10-15 mL/unit). Cryoprecipitate contains concentrated levels of fibrinogen (an average of 250 mg), von Willebrand factor, factor VIII (80 IU), factor XIII, and fibronectin. As such, Cryoprecipitate has relatively limited indications, but is particularly useful because of its small volume and high fibrinogen content. In fact, the majority of Cryo is used for the replacement of fibrinogen in the settings of massive blood loss/massive transfusion, fibrinogen consumption (e.g. in hemorrhage or DIC), or in patients with impaired fibrinogen function (dysfibrinogenemia). Cryo has also been shown to be effective in the treatment of bleeding associated with uremia, likely due to its von Willebrand factor and fibrinogen content.

For the patient with hypofibrinogenemia of any cause, an accepted transfusion trigger is a fibrinogen level <100 mg/dL. Although complex formulae exist to calculate exact doses, for most adults with significant hypofibrinogenemia or for those with DIC, a 10 unit pool (total volume = ~100-150 mL) should be sufficient to promote hemostasis. This dose is also sufficient to address uremic bleeding in adults. Single units or small doses (at 10-15 mL/kg) have been used for children. Frequent monitoring of coagulation factors (particularly fibrinogen) is recommended to determine the need for future Cryo doses.

SUMMARY:

Blood products are an important part of the management of in- and out-patients. With appropriate knowledge of evidence-based literature and dosing guidelines, clinicians can safely and effectively transfuse their patients while maximizing the therapeutic benefit of this intervention.

Marie E. Peddinghaus, MD, Clinical Fellow
Laboratory Medicine (Transfusion Medicine)
Christopher Anthony Tormey, MD

Instructor, Laboratory Medicine

GENERAL REFERENCES:


Special Modification of Blood Products

Blood products are routinely used as a life-saving measure for critically ill patients or as chronic support for patients with anemia or those at risk of developing bleeding. Unfortunately, complications associated with transfusion are still a relatively common problem. There are several well-documented risks associated with blood product transfusion, particularly in populations with known immune deficiencies. As such, the YNHH Blood Bank has instituted various procedures including leukoreduction, unit washing/saline re-suspension, and gamma irradiation. Each of these special procedures, and the specific conditions and risks that they address, are discussed in more detail below.

Leukoreduction:

Currently, cellular blood components such as red blood cells (RBCs) and platelets at YNHH are universally leukoreduced. This means that individual units contain less than 5 x 10^6 donor leukocytes in the final product. Leukoreduction is accomplished by filtration of blood through high-efficiency devices which trap white cells, preventing their passage to the final collected product or through the use of leukocyte
removal software on automated apheresis devices. Filtration is performed immediately following collection and/or prior to blood component storage (pre-storage leukoreduction). There are several important benefits associated with leukoreduction. Perhaps the most important advantage of this process is that it reduces recipient exposure to HLA antigens present on white cells, greatly diminishing the risk of alloimmunization to HLA antigens, and thereby reducing the incidence of immune mediated platelet refractoriness (HLA antigens are also present on platelets). A reduction in HLA alloimmunization is of particular importance to oncology and other patients who are chronically transfused with platelet products. In addition, leukoreduction also drastically reduces circulating cytomegalovirus (CMV) which is typically harbored in white cells. As such, leukoreduced products are considered CMV-safe and are associated with reduced transmission of this virus. Yet another benefit of leukoreduction is a decrease in the occurrence of febrile non-hemolytic transfusion reactions which are believed to be mediated by cytokines secreted by white cells during blood storage or after transfusion.

**Gamma Irradiation:**

Significantly immunosuppressed patients are at an increased risk for transfusion-associated graft-vs-host disease (TA-GVHD). In this entity, and unlike post-transplant GVHD, mortality rates approach 100% because lymphocytes from donor units engraft in recipients and mediate a severe response. Therefore, prevention of TA-GVHD is of utmost importance for immunosuppressed patients. Exposure of cellular blood components to gamma rays inactivates the regenerative capabilities of donor lymphocytes and is extremely effective at eliminating the risk of TA-GVHD for immunosuppressed transfusion recipients. While an important procedure, irradiation carries some disadvantages including potassium leakage from the RBC membrane and a shortened RBC unit shelf life. In addition, providing irradiated cellular products can add cost and preparation time. While most patients can safely receive irradiated products, it is only indicated for selected patient populations. As such, YNHH has specific indications for appropriate usage of irradiated products including: patients with hematologic malignancies, patients who are currently receiving high dose chemotherapy, solid organ and stem cell transplant patients, directed donations from blood relatives, and patients with congenital cellular immune deficiency disorders. In addition we irradiate all cellular components for patients less than 4 months of age.

**Cellular Washing / Saline Re-suspension:**

Occasionally, the residual plasma contained in RBC and platelet units may contain proteins or other antigens which can mediate severe allergic or even anaphylactic reactions. As such, a patient who demonstrates such a reaction following transfusion may benefit from washing of RBCs or saline re-suspension of platelets. Washing of RBCs removes up to 99% of plasma proteins, electrolytes, and antibodies. The process of washing blood components, while efficient, requires an additional 30-60 minutes of additional preparation time in the blood bank. For platelet products, washing can result in significant loss of platelets in addition to causing some platelet dysfunction. Thus, saline re-suspended platelets (wherein platelets are centrifuged, supernatant plasma decanted, and remaining platelets re-suspended in saline) are often provided in lieu of washing. As mentioned previously, washing or saline replacement of blood products is only appropriate for patients who demonstrate severe or repeated allergic reactions to blood product infusion. The YNHH Blood Bank recommends this option for patients who have had documented severe allergic reactions to blood products, and in patients with IgA deficiency and documented anti-IgA antibodies. In addition, washing can also be used as a tool to prevent hyperkalemia in at risk pediatric patients.

In summary, it is important to provide appropriate blood products to each blood recipient at our facility. If you have questions regarding special modifications of blood products, we encourage you to contact our Laboratory Medicine residents/fellows and Transfusion Medicine attendings, Drs. Snyder, Wu, and Tormey(laboratory phone 688-2443), who are available at all times for consultation.

Megan Selbst, MD, Resident
Laboratory Medicine and Pathology

Christopher Tormey, MD
Instructor, Laboratory Medicine

General References:


