Patient Blood Management: Optimizing Transfusion Benefits and Recognizing When Transfusions Are Helpful

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Introduction

This paper describes the application of the principles of patient blood management, or PBM, which is an evidence-based, multidisciplinary approach to optimizing the care of patients who might need a transfusion.

The three basic concepts of patient blood management (PBM) incorporate good medical logic:

- Optimize the patient's red cell mass.
- Minimize blood loss.
- If transfusions are needed, transfuse wisely.

For each of these basic principles there are several strategies that may be employed to promote PBM:

- Prepare and manage a patient, whenever possible, so that transfusion thresholds are less likely to be approached. This includes assessing the patient for anemia prior to elective surgery and taking steps to correct the problem.
- Reduce blood loss through use of certain pharmaceuticals such as tranexamic acid (TXA) in orthopedic surgery; use meticulous surgical techniques and minimize the frequency of laboratory testing and amount of blood collected for lab tests.
- Manage the patient so that the physiologic impact of the anemia (that is, reduction in the red blood cell count) or other abnormality is minimized. If a transfusion is needed, make transfusion decisions based on the best available, objective evidence.

This paper reviews some of the reasons that the risk-benefit equation may not favor transfusion as frequently as some might have previously thought and illustrates the principles of PBM.

The life-saving value of transfusion is easily recognized in many circumstances. For an exsanguinating trauma patient, red blood cell (RBC) transfusions ensure adequate oxygen availability to allow surgical repair. Platelet transfusions allow thrombocytopenic patients to

complete therapy with a reduced risk of hemorrhage. Transfusion of plasma can correct significant coagulopathy and minimize the risk of bleeding. In extreme cases, the benefits of transfusion are obvious, any risks minimal by comparison, and any complications managed as part of the patient's course of therapy.

Most transfusions are not given in such circumstances, however. A laboratory test value, whether it be a hemoglobin concentration, a platelet count, or a prothrombin time/international normalized ratio (INR), is usually the rationale cited for prophylactic transfusion. "I don't want my patient to have a myocardial infarction" or "I don't want my patient to bleed during the procedure" can often be elicited from the ordering physician.

These goals are certainly laudable since the damage of myocardial necrosis or the complications from hemorrhage can be significant and/or irreversible. In any equation of therapy, and particularly when a prophylactic intervention is being considered, the potential benefits associated with the therapy must be weighed in comparison to the probability of the morbidity that the therapy is intended to avoid as well as the probability of an untoward effect arising from the therapy itself.

In the case of transfusion, the potential complications are often considered in terms of transfusion reactions. The most common of these—febrile and urticarial reactions—are regarded by some clinicians as trivial and easily managed, and the most feared—transfusion-transmitted infections (TTI) —are regarded today as vanishingly rare and beyond the experience of most physicians. As a result, blood may be administered with little regard for risk.

However, while transfusions are certainly safer today than at any time in medical history, these recognized risks have a finite, non-zero probability, and their consequences can be catastrophic. For example, transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) have remained the two most common causes of transfusion-associated fatality reported to the United States (US) Food and Drug Administration (FDA).[1]

The last 15 years have seen an interesting shift in the source of concerns about transfusion. With dramatic reductions in the risks of transmitting the most-notable pathogens, such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV), concern has shifted to other risks, including TRALI and bacterial contamination of platelets.

In the United States, most blood suppliers now provide plasma and apheresis platelets from males, females who have never been pregnant, or females who have been shown to lack HLA antibodies to mitigate the risk of TRALI. This strategy has reduced the incidence of TRALI to 1:10,000 units transfused.[2] Red blood cells now are the most frequently implicated product associated with TRALI.

As the incidence of TRALI has decreased, the most common cause of transfusion-associated death is now TACO. Platelets and plasma components are associated with a TACO incidence of approximately 1% and RBCs with an incidence of 2.7%.[2] TACO occurs most commonly in patients at the extremes of age and in those with congestive heart failure.

Bacterial contamination is primarily a concern in platelet units because of their storage at room temperature. Because of difficulties recognizing transfusion as the source of infection in a patient population already prone to fevers and comorbidities, the risk of posttransfusion sepsis may not be recognized by most clinicians. Steps taken to reduce this risk, such as culturing of apheresis platelet units, which substantially reduces but does not eliminate risk, have further pushed this risk to the back of physicians' minds. However, the risk continues to remain. Some centers have implemented point-of-release rapid bacterial testing or treatment of apheresis platelet units with pathogen reduction technology to further minimize this risk.

Over the years physicians have been concerned about intrinsic risks of transfusion, particularly certain byproducts of red cell metabolism that may accumulate in the container during the red cell storage period. Studies have not shown a clinically significant benefit from transfusion of fresh RBCs (less than 10 days). A recent meta-analysis of 13 trials that enrolled more than 5,000 participants found no impact of fresh vs older RBCs on mortality or adverse events.[3]

The costs of transfusion also deserve mention. Physicians base therapeutic decisions on patient outcomes, not costs. However, current healthcare economics require that careful consideration be given to alternative modalities that yield equivalent outcomes. A transfusion that improves the patient's outcome is easily justified; a dubious risk-benefit ratio, however, cannot be used to justify a large expense. Additionally, transfusions are expensive. The acquisition cost of a voluntarily donated unit that is fully tested may appear a great bargain, but tallying hospital fixed costs for storage and handling, pre-transfusion testing, bedside management costs, and those related to management of complications easily increases the cost of transfusion to three or four times that of the unit itself.[4] If this brings useful benefit to the patient, the cost is easily justified. If that benefit is illusory, a different pattern of practice may not only be less costly but provide a better outcome.

In addition to the patient safety risks and increased costs associated with blood transfusions, it should be remembered that the United States blood supply is a limited resource obtained entirely from volunteer donors. Blood shortages have, and likely will continue to occur, particularly for the universal donor group O-negative RBCs, group AB plasma, antigen-matched RBCs, and apheresis platelets. If the evidence-based decision-making process does not clearly show that a transfusion is appropriate for a given patient, transfusion should be avoided. This will help to ensure that adequate blood products will be available for the patients who truly need them the most.

Red Blood Cells

On the other side of the ledger, the presumed benefits of transfusion may be illusory and the underlying risk of the morbidity that was to be avoided may be less than was thought. As a result, the balance between risk and benefit may not tilt in the presumed direction. A variety of prospective randomized clinical trials, such as the "Transfusion Requirements in Critical Care" (TRICC) trial studying ICU patients,[5] the "Effects of Fluoxetine on Functional Outcomes after Acute Stroke" FOCUS trial studying patients with hip fracture and coronary artery disease,[6] the "Transfusion Requirements in Septic Shock" (TRISS) trial studying patients with septic shock,[7] and the Transfusion Requirements in Cardiac Surgery (TRICS) trial in cardiac surgery patients,[8]

have all investigated the effect of applying a "conservative" (7-8g/dL) as opposed to a "liberal" (9-10g/dL) threshold for red cell transfusions. For all of these studies, either the conservative approach was as safe and efficacious or was more so than the liberal one. Such outcomes have bolstered the contention that a liberal transfusion strategy is not beneficial: "More is not better."

In 2016, the AABB published RBC transfusion guidelines based on 31 randomized clinical trials (RCTs) that included 12,587 patients.[3] An expert panel recommended a restrictive RBC transfusion threshold in which transfusion was not indicated until the hemoglobin level was 7g/dL for hospitalized adult patients who were hemodynamically stable, including critically ill patients, rather than a liberal threshold of 10g/dL. For patients undergoing orthopedic surgery or cardiac surgery and those with preexisting cardiovascular disease, the AABB recommended a restrictive RBC transfusion threshold at a hemoglobin level of 8g/dL.

The primary outcome of 30-day mortality was reported in 23 RCTs.[3] The TRICS trial compared a restrictive red cell transfusion threshold of less than 7.5 g/dL to a liberal threshold of less than 9.5 g/dL in the operating room or ICU and less than 8.5 g/dL in the non-ICU ward for high-risk cardiac surgery patients.[8] This study found that patients who were transfused restrictively received fewer red blood cell transfusions with no significant difference in morbidity or mortality compared to patients transfused with a liberal strategy. Similarly, the FOCUS trial studying patients undergoing surgical repair of hip fracture did not gain any advantage in terms of earlier recuperation of mobility or enjoy lower rates of cardiovascular complications from a liberal transfusion threshold despite the advanced age of the patients studied [mean age of the study population was 81.6 years (range, 51 to 103)].[6] For all other outcomes evaluated, there was no evidence to suggest that patients were harmed by restrictive transfusion protocols, although the quality of the evidence was low for the outcomes of congestive heart failure and rebleeding.

A restrictive transfusion threshold approach was associated with reductions in blood use, associated expense, and uncommon but potentially serious adverse events. The AABB did not make a recommendation for a transfusion threshold in patients treated for hematologic or oncologic disorders and for those with severe thrombocytopenia who were at risk of bleeding or for those with chronic transfusion–dependent anemia. There have not been RCTs performed in patients with chronic transfusion–dependent anemia. The risks and benefits (ie, improved function, less fatigue) are different for patients receiving chronic transfusions outside the hospital than hospitalized patients in acute care settings.

The application of restrictive transfusion threshold is useful in determining when to transfuse; however, even with the appropriate adherence to the restrictive thresholds, over-transfusion can continue to occur when/if more units than needed are transfused. In parallel with the application of restrictive thresholds the use of single-unit transfusion has become common practice.[9] In 2014 the AABB's transfusion contributions to the Choosing Wisely's campaign provided the general recommendation "do not transfuse more units than absolutely necessary."[10] This was followed-up by the "Why give 2 when 1 will do" campaign to further stress the use of single-unit transfusion as a means of reducing patients exposure to allogeneic blood.[11] These efforts have resulted in even further reductions in blood use over the application of restrictive thresholds alone.

As with all other clinical guidelines the success of transfusion-related guidelines is only as good as the end-user provider's compliance allows. Improvements in PBM programs and the correct use of guidelines can be enhanced based on several types of interventions. Educational efforts, use of audits of providers practice, and the use of decision-support systems have all be used with varying degrees of success. With the increasing utilization of electronic medical records (EMRs) the application of decision support within the EMR or "electronic decision support" (EDS) to promote appropriate utilization of restrictive transfusion threshold and the optimal use of single-unit transfusions has been shown to improve PBM efforts. These EDS tools can be as simple as restricting/defaulting transfusion orders to a single unit at a time with required re-evaluation prior to release of any additional units.[12] One of the most well studied EDS tools is the use of alerts with embedded education within the EMRs blood orders that present when the patient's pretransfusion hemoglobin or hematocrit do not comply with restrictive guidelines.[13-15] Lastly, the use of blood mathematic algorithms to provide dosing recommendations in units can further prevent over-transfusion by discouraging transfusion beyond restrictive thresholds and by favoring the use of single-unit transfusions.[16]

Platelets

Prophylactic administration of platelets has long been assumed to be beneficial in avoiding hemorrhage in thrombocytopenic patients. The Platelet Dose Study (PLADO) transfused patients with one of three doses of platelets: low, medium, and high.[17] Bleeding of World Health Organization grade 2 or higher occurred on 25% of the study days in which morning platelet counts were 5,000 per microliter or lower, as compared with 17% of study days on which platelet counts were between 6,000 and 80,000 per microliter. Among the three platelet dose groups there was not a significant difference in grade 2 or higher bleeding. The median number of platelets transfused was significantly lower in the low-dose group than in the medium-dose or high-dose group, which led to shorter interval between transfusion episodes and significantly higher median number of platelet transfusions given in the low-dose group. In table 1, Summary of Recommendations for Prophylactic Platelet Transfusion in Adults, the authors concluded that different dose strategies for prophylactic platelet transfusion had no effect on the incidence of clinically significant bleeding[2].

TABLE 1. Summary of AABB Recommendations for Prophylactic Platelet Transfusion in Adults[2]

Clinical Setting	Platelet Transfusion May Be Indicated for:	Strength of Recommendation	Quality of Evidence
Therapy-related hypoproliferative thrombocytopenia	Platelet count ≤10,000/μL	Strong	Moderate
Central venous catheter placement	Platelet count <20,000/μL	Weak	Low
Diagnostic lumbar puncture	Platelet count <50,000/μL*	Weak	Very low
Major elective nonneuraxial surgery	Platelet count <50,000/μL	Weak	Very low
Cardiac surgery with bypass	Perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction. Routine platelet prophylaxis not recommended.	Weak	Very low
Intracranial hemorrhage on antiplatelet therapy	Insufficient evidence for recommendation	Uncertain	Very low

*Clinical judgment should be used for patients with platelet counts between 20,000 and 50,000/μL.

For patients with active bleeding, there is no high-quality evidence for guidance, although it is often recommended to maintain the platelet count above 50,000 per microliter. Using empiric decisions, some clinicians will choose to use 100,000/μL as the threshold for ophthalmologic and neurologic surgery. In patients with platelet dysfunction, either due to congenital or acquired causes, platelet transfusion may be acceptable even at normal platelet counts and the decision should be based upon the patient's clinical condition and platelet function studies.

Different institutions may use different types of platelet products, which are clinically equivalent in terms of increasing the patient's platelet count:

- Apheresis platelets collected from one donor and stored in 100% donor plasma.
- Apheresis platelets stored in platelet additive solution, or PAS.
- Pathogen-reduced apheresis platelets, treated to reduce the likelihood of transfusion-transmitted infection.
- Pooled platelets collected from 4-6 donors and pooled into a single unit (most commonly pooled at the blood center in a closed system).
- Cold stored platelets indicated for actively bleeding patients.

<u>Plasma</u>

In the US, the terms "plasma" and "fresh-frozen plasma" are often used interchangeably. Taking into account product manufacturing and labelling requirements, "plasma" usually refers to multiple different products: plasma frozen within 8 hours of collection (FFP), plasma frozen within 24 hours of collection (FP24), thawed FFP or FP24 plasma (thawed plasma), solvent/detergent plasma (S/D plasma), and plasma that has never been frozen (liquid plasma). It is common practice for a transfusion service to issue FFP, FP24, and thawed plasma to be used interchangeably. Plasma is a composite blood product with many different components. As such, plasma transfusion practices include diverse clinical scenarios and indications. High-quality evidence guiding plasma transfusion remains more limited relative to RBC and platelet transfusion. In a Cochrane systematic review, of 843 references identified in the literature, none of the clinical trials satisfied inclusion criteria for review.[18,19] Additionally, since plasma is a composite product used to replace diverse specific components, targeted replacement therapies such as factor concentrates are becoming increasingly available and taking the place of plasma transfusion in certain settings (see plasma alternatives below).

Generally, plasma is indicated for coagulation factor replacement when more targeted therapies are not available. A clear example of this type of indication is massive transfusion. Massive transfusion can lead to global coagulation factor deficiency that can be exacerbated with crystalloid infusion. Plasma transfusion in this setting provides a relatively balanced bolus of coagulation factors mitigating worsening coagulopathy.[20-24] Plasma is commonly used in trauma situations, with some high-quality evidence pointing toward improved survival with early plasma transfusion. Another plasma indication example includes reversal of warfarin anticoagulation in patients with intracranial hemorrhage. Plasma can provide immediate replacement of vitamin K-dependent coagulation factors. It is important to note, however, that lower volume-specific factor concentrates are now approved for urgent warfarin reversal (see section on plasma alternatives below). Plasma is also indicated as a replacement fluid during plasma exchange procedures for treatment of thrombotic thrombocytopenic purpura (TTP). In this setting, plasma serves as a source for A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motifs, member 13 (ADAMTS-13), the enzyme deficient in TTP patients.

Plasma may also be transfused prior to invasive procedures when the INR is > 2.0 and for congenital factor deficiencies for which no specific factor concentrates are available. Plasma is generally not indicated for situations that have typically resulted in prophylactic plasma infusion, when coagulopathy or bleeding are absent, and where the risk of lung injury and possible increased mortality outweighs the potential benefit. More clinical trials are needed in this area, and some authors have argued that plasma is a superior product as a volume expander in the context of volume-depleted shock even after coagulopathy has been addressed.[24] An audit of plasma utilization was conducted in the Canadian province of Ontario. Of 573 requests, 164 (28.6%) were deemed inappropriate most often because they were administered to patients with an INR below 1.5 or they were administered in the absence of bleeding or emergency surgery.[22] When pre-procedure correction of coagulopathy is required, plasma should be given immediately before the procedure. The appropriate dose should be 10 to 20 mL/kg based upon the patient's size. Multiple (2-4) units are considered acceptable, taking into account the patient's tolerance for transfusion volume. Measurement of coagulation parameters should occur before and within 5 hours after

transfusion, as Factor VII has a biologic half-life of only 5 hours in vivo. Laboratory readings obtained after 5 hours will not be a true reflection on the effectiveness of transfusion.

FFP Alternatives

PCC (Kcentra®) is FDA approved for immediate warfarin reversal in patients with acute major bleeding or need for urgent surgery or invasive procedure, Kcentra is a balanced, human derived concentrate that contains a defined concentration of four vitamin K-dependent clotting factors (II, VII, IX, and X) and the thrombo-inhibitor proteins C and S. The coagulation factors are not activated and therefore have a lower thrombotic risk profile in comparison to NovoSeven (concentrated activated factor VII). Dosing of Kcentra is can be calculated based on the INR of the patient, but many hospitals now use fixed dosing and then repeat based on INR or clinical bleeding. Fixed dosing has been found to be safe, effective, and more efficient than dosing by INR.[25-27] Kcentra will have approximately 5 hours of coverage (based on Factor VII half-life). If there is doubt as to whether the patient is adequately corrected, a STAT INR can be obtained. A risk of repeated administration of Kcentra is the cumulative dose of factor II and its long half-life (~60 hours), potentially leading to a prothrombotic state. The most serious side effect of these agents is of course thrombotic events. Kcentra contains heparin and is contraindicated in patients with heparin-induced thrombocytopenia.

Fibrinogen Concentrates (RiaSTAP and Fibryga)

Fibrinogen concentrates are FDA approved for treatment of acute bleeding in individuals with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. These concentrates are also expensive, which may be a consideration prior to their utilization in any scenario outside of life-threatening cases.

Factor VII or rFVIIa (NovoSeven ®)

Factor VIIa is utilized in the treatment of active bleeding or preventing bleeding in patients with hemophilia A or B with inhibitors as well as acquired hemophilia. The same use is indicated in patients with FVII deficiency. The most common and serious side effect of FVII is thrombosis.

Antifibrinolytics

Amicar (aminocaproic acid) and TXA are competitive inhibitors of plasminogen activation and used to decrease fibrinolysis and increase existing clot stability at the site of injury. TXA is 10 times more potent than Amicar and has the added benefit of not requiring a dedicated line and it can be administered intravenously 2-3 times daily. FDA-approved use of TXA is for heavy menstrual bleeding and short-term prevention of bleeding in patients with hemophilia. This includes tooth extractions in patients with hemophilia as well as menorrhagia in these patients. These drugs do not have the same risk profile of factor VII or PCCs and may be used in conjunction with blood products and blood product alternatives.

Cryoprecipitate

Cryoprecipitated antihemophilic factor (AHF) is a plasma-derived blood product for transfusion that is relatively enriched for fibrinogen (factor I), factor VIII, factor XIII, von Willebrand factor, and fibronectin. Each unit of cryoprecipitate contains a minimum of 80 IU of factor VIII and at least 150 mg of fibrinogen, in addition to significant amounts of von Willebrand factor and factor XIII.

Cryoprecipitate is stored frozen at -18 C or colder and must be thawed prior to issue and transfusion. It must be transfused within 4 hours after thawing. Current practices surrounding ABO compatibility for cryoprecipitate are variable; however, a recent study supported the safety of cryoprecipitate transfusion without ABO matching in adult recipients.[28] ABO-matched cryoprecipitate may still be preferred for neonates and small children or for adults receiving a large volume of cryoprecipitate in order to avoid passive transfer of ABO antibodies that could lead to hemolysis.

Cryoprecipitate can be provided as single units or as "pools" containing 5 or more units. The clinician should check with the local hospital transfusion service or blood supplier in order to determine the correct dosage for a patient. For adult patients, standard dosage is a pre-pool of 5 or 10 units of cryoprecipitate. For neonatal/pediatric patients transfusion is based on weight:

Dosing of small volumes in Neonatal and Pediatric Patients: 1-2 units/10Kg. Expected increment of 60-100 mg/dL rise in fibrinogen (assuming 100% recovery).

Cryoprecipitate transfusions are primarily used to treat conditions resulting from 1) decreased or dysfunctional fibrinogen (congenital or acquired) or 2) factor XIII deficiency, if Factor XIII concentrate [eg, Corifact (CSL Behring)] is not available. Cryoprecipitate is also given in conjunction with platelets and FFP to treat disseminated intravascular coagulation (DIC). Typically, 1 unit is sufficient to achieve hemostatic levels in an infant.

Cryoprecipitate transfusion is not recommended for patients with Factor VIII deficiency because standard therapy for this condition is infusion of recombinant or virus-inactivate, monoclonal-antibody-purify, plasma-derived Factor VIII products.

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